

At the high dose (1.2 µg), the glycoPEGylated rFSH had somewhat higher *in vivo* activity than the unPEGylated rFSH.

G-CSF

28. GlycoPEGylation of G-CSF produced in CHO cells

Preparation of Asialo-Granulocyte-Colony Stimulation Factor (G-CSF). G-CSF produced in CHO cells is dissolved at 2.5 mg/mL in 50 mM Tris 50 mM Tris-HCl pH 7.4, 0.15 M NaCl, 5 mM CaCl₂ and concentrated to 500 µL in a Centricon Plus 20 centrifugal filter. The solution is incubated with 300 mU/mL Neuraminidase II (*Vibrio cholerae*) for 16 hours at 32 °C. To monitor the reaction a small aliquot of the reaction is diluted with the appropriate buffer and a IEF gel performed. The reaction mixture is then added to prewashed N-(*p*-aminophenyl)oxamic acid-agarose conjugate (800 µL/mL reaction volume) and the washed beads gently rotated for 24 hours at 4 °C. The mixture is centrifuged at 10,000 rpm and the supernatant was collected. The beads are washed 3 times with Tris-EDTA buffer, once with 0.4 mL Tris-EDTA buffer and once with 0.2 mL of the Tris-EDTA buffer and all supernatants are pooled. The supernatant is dialyzed at 4 °C against 50 mM Tris -HCl pH 7.4, 1 M NaCl, 0.05% NaN₃ and then twice more against 50 mM Tris -HCl pH 7.4, 1 M NaCl, 0.05% NaN₃. The dialyzed solution is then concentrated using a Centricon Plus 20 centrifugal filter and stored at -20 °C. The conditions for the IEF gel were run according to the procedures and reagents provided by Invitrogen. Samples of native and desialylated G-CSF are dialyzed against water and analyzed by MALDI-TOF MS.

Preparation of G-CSF-(alpha2,3)-Sialyl-PEG. Desialylated G-CSF was dissolved at 2.5 mg/mL in 50 mM Tris-HCl, 0.15 M NaCl, 0.05% NaN₃, pH 7.2. The solution is incubated with 1 mM CMP-sialic acid-PEG and 0.1 U/mL of ST3Gal1 at 32°C for 2 days. To monitor the incorporation of sialic acid-PEG, a small aliquot of the reaction had CMP-SA-PEG-fluorescent ligand added; the label incorporated into the peptide is separated from the free label by gel filtration on a Toso Haas G3000SW analytical column using PBS buffer (pH 7.1). The fluorescent label incorporation into the peptide is quantitated using an in-line fluorescent detector. After 2 days, the reaction mixture is purified using a Toso Haas G3000SW preparative column using PBS buffer (pH 7.1) and collecting fractions based on UV absorption. The product of the reaction is analyzed using SDS-PAGE and IEF analysis

according to the procedures and reagents supplied by Invitrogen. Samples of native and PEGylated G-CSF are dialyzed against water and analyzed by MALDI-TOF MS.

Preparation of G-CSF-(alpha2,8)-Sialyl-PEG. G-CSF produced in CHO cells, which contains an alpha2,3-sialylated O-linked glycan, is dissolved at 2.5 mg/mL in 50 mM Tris-HCl, 0.15 M NaCl, 0.05% NaN₃, pH 7.2. The solution is incubated with 1 mM CMP-sialic acid-PEG and 0.1 U/mL of CST-II at 32°C for 2 days. To monitor the incorporation of sialic acid-PEG, a small aliquot of the reaction has CMP-SA-PEG-fluorescent ligand added; the label incorporated into the peptide is separated from the free label by gel filtration on a Toso Haas G3000SW analytical column using PBS buffer (pH 7.1). The fluorescent label incorporation into the peptide is quantitated using an in-line fluorescent detector. After 2 days, the reaction mixture is purified using a Toso Haas G3000SW preparative column using PBS buffer (pH 7.1) and collecting fractions based on UV absorption. The product of the reaction is analyzed using SDS-PAGE and IEF analysis according to the procedures and reagents supplied by Invitrogen. Samples of native and PEGylated G-CSF are dialyzed against water and analyzed by MALDI-TOF MS.

Preparation of G-CSF-(alpha2,6)-Sialyl-PEG. G-CSF, containing only O-linked GalNAc, is dissolved at 2.5 mg/mL in 50 mM Tris-HCl, 0.15 M NaCl, 0.05% NaN₃, pH 7.2. The solution is incubated with 1 mM CMP-sialic acid-PEG and 0.1 U/mL of ST6GalNAcI or II at 32°C for 2 days. To monitor the incorporation of sialic acid-PEG, a small aliquot of the reaction has CMP-SA-PEG-fluorescent ligand added; the label incorporated into the peptide is separated from the free label by gel filtration on a Toso Haas G3000SW analytical column using PBS buffer (pH 7.1). The fluorescent label incorporation into the peptide is quantitated using an in-line fluorescent detector. After 2 days, the reaction mixture is purified using a Toso Haas G3000SW preparative column using PBS buffer (pH 7.1) and collecting fractions based on UV absorption. The product of the reaction is analyzed using SDS-PAGE and IEF analysis according to the procedures and reagents supplied by Invitrogen. Samples of native and PEGylated G-CSF are dialyzed against water and analyzed by MALDI-TOF MS.

G-CSF produced in CHO cells was treated with Arthrobacter sialidase and was then purified by size exclusion on Superdex75 and was treated with ST3Gal1 or ST3 Gal2 and then with CMP-SA-PEG 20Kda. The resulting molecule was purified by ion exchange and

gel filtration and analysis by SDS PAGE demonstrated that the PEGylation was complete. This is the first demonstration of glycoPEGylation of an O-linked glycan.

Glucocerebrosidase

29. Glucocerebrosidase-mannose-6-phosphate produced in CHO cells

This example sets forth the procedure to glycoconjugate mannose-6-phosphate to a peptide produced in CHO cells such as glucocerebrosidase.

Preparation of asialo-glucoceramidase. Glucocerebrosidase produced in CHO cells is dissolved at 2.5 mg/mL in 50 mM Tris 50 mM Tris-HCl pH 7.4, 0.15 M NaCl, and is incubated with 300 mU/mL sialidase-agarose conjugate for 16 hours at 32 °C. To monitor the reaction a small aliquot of the reaction is diluted with the appropriate buffer and a IEF gel and SDS-PAGE performed according to Invitrogen procedures. The mixture is centrifuged at 10,000 rpm and the supernatant is collected. The beads are washed 3 times with Tris-EDTA buffer, once with 0.4 mL Tris-EDTA buffer, and once with 0.2 mL of the Tris-EDTA buffer. All supernatants are pooled. The supernatant is dialyzed at 4 °C against 50 mM Tris-HCl pH 7.4, 1 M NaCl, 0.05% NaN₃ and then twice more against 50 mM Tris-HCl pH 7.4, 1 M NaCl, 0.05% NaN₃. The dialyzed solution is then concentrated using a Centricon Plus 20 centrifugal filter. The product of the reaction is analyzed using SDS-PAGE and IEF analysis according to the procedures and reagents supplied by Invitrogen. Samples are dialyzed against water and analyzed by MALDI-TOF MS.

Preparation of Glucocerebrosidase-SA-linker-Mannose-6-phosphate (procedure 1).

Asialo-glucocerebrosidase from above is dissolved at 2.5 mg/mL in 50 mM Tris-HCl, 0.15 M NaCl, 0.05% NaN₃, pH 7.2. The solution is incubated with 1 mM CMP-sialic acid-linker-Man-6-phosphate and 0.1 U/mL of ST3Gal3 at 32°C for 2 days. To monitor the incorporation of sialic acid-linker-Man-6-phosphate, a small aliquot of the reaction had CMP-SA-PEG-fluorescent ligand added; the label incorporated into the peptide is separated from the free label by gel filtration on a Toso Haas TSK-Gel-3000 analytical column using PBS buffer (pH 7.1). The fluorescent label incorporation into the peptide is quantitated using an in-line fluorescent detector. When the reaction is complete, the reaction mixture is purified using a Toso Haas TSK-Gel-3000 preparative column using PBS buffer (pH 7.1) and collecting fractions based on UV absorption. The product of the reaction is analyzed using

SDS-PAGE and IEF analysis according to the procedures and reagents supplied by Invitrogen. Samples are dialyzed against water and analyzed by MALDI-TOF MS.

Preparation of Glucocerebrosidase-SA-linker-Mannose-6-phosphate (procedure

2). Glucocerebrosidase, produced in CHO but incompletely sialylated, is dissolved at 2.5 mg/mL in 50 mM Tris-HCl, 0.15 M NaCl, 0.05% NaN₃, pH 7.2. The solution is incubated with 1 mM CMP-sialic acid-linker-Man-6-phosphate and 0.1 U/mL of ST3Gal3 at 32°C for 2 days. To monitor the incorporation of sialic acid-linker-Man-6-phosphate, a small aliquot of the reaction had CMP-SA-PEG-fluorescent ligand added; the label incorporated into the peptide is separated from the free label by gel filtration on a Toso Haas TSK-Gel-3000 analytical column using PBS buffer (pH 7.1). The fluorescent label incorporation into the peptide is quantitated using an in-line fluorescent detector. When the reaction is complete, the reaction mixture is purified using a Toso Haas TSK-Gel-3000 preparative column using PBS buffer (pH 7.1) and collecting fractions based on UV absorption. The product of the reaction is analyzed using SDS-PAGE and IEF analysis according to the procedures and reagents supplied by Invitrogen. Samples are dialyzed against water and analyzed by MALDI-TOF MS.

30. Glucocerebrosidase-transferrin

This example sets forth the procedures for the glycoconjugation of proteins, and in particular, transferrin is glycoconjugated to glucocerebrosidase. The GlcNAc-ASN structures are created on glucoceraminidase, and Transferrin-SA-Linker-Gal-UDP is conjugated to GNDF GlcNAc-ASN structures using galactosyltransferase.

Preparation of GlcNAc-glucocerebrosidase (Cerezyme™). Cerezyme™ (glucocerebrosidase) produced in CHO cells is dissolved at 2.5 mg/mL in 50 mM Tris 50 mM Tris-HCl pH 7.4, 0.15 M NaCl, and is incubated with 300 mU/mL Endo-H-agarose conjugate for 16 hours at 32 °C. To monitor the reaction a small aliquot of the reaction is diluted with the appropriate buffer and a IEF gel and SDS-PAGE performed according to Invitrogen procedures. The mixture is centrifuged at 10,000 rpm and the supernatant is collected. The beads are washed 3 times with Tris-EDTA buffer, once with 0.4 mL Tris-EDTA buffer and once with 0.2 mL of the Tris-EDTA buffer and all supernatants are pooled. The supernatant is dialyzed at 4 °C against 50 mM Tris -HCl pH 7.4, 1 M NaCl, 0.05% NaN₃ and then twice

more against 50 mM Tris-HCl pH 7.4, 1 M NaCl, 0.05% NaN₃. The dialyzed solution is then concentrated using a Centricon Plus 20 centrifugal filter. The product of the reaction is analyzed using SDS-PAGE and IEF analysis according to the procedures and reagents supplied by Invitrogen. Samples are dialyzed against water and analyzed by MALDI-TOF MS.

Preparation of Transferrin-SA-Linker-Gal-glucocerebrosidase. Transferrin-SA-Linker-Gal-UDP from above is dissolved at 2.5 mg/mL in 50 mM Tris-HCl, 0.15 M NaCl, 5 mM MnCl₂, 0.05% NaN₃, pH 7.2. The solution is incubated with 2.5 mg/mL GlcNAc-glucocerebrosidase and 0.1 U/mL of galactosyltransferase at 32°C for 2 days. To monitor the incorporation of glucocerebrosidase, the peptide is separated by gel filtration on a Toso Haas G3000SW analytical column using PBS buffer (pH 7.1) and the product detected by UV absorption. The reaction mixture is then purified using a Toso Haas G3000SW preparative column using PBS buffer (pH 7.1) collecting fractions based on UV absorption. The product of the reaction is analyzed using SDS-PAGE and IEF analysis according to the procedures and reagents supplied by Invitrogen. Samples are dialyzed against water and analyzed by MALDI-TOF MS.

GM-CSF

31. Generation and PEGylation of GlcNAc-ASN Structures: GM-CSF produced in *Saccharomyces*

This example sets forth the preparation of Tissue-type Activator with PEGylated GlcNAc-Asn structures.

Recombinant GM-CSF expressed in yeast is expected to contain 2 N-linked and 2 O-linked glycans. The N-linked glycans should be of the branched mannan type. This recombinant glycoprotein is treated with an endoglycosidase from the group consisting of endoglycosidase H, endoglycosidase-F1, endoglycosidase-F2, endoglycosidase-F3, endoglycosidase-M either alone or in combination with mannosidases I, II and III to generate GlcNAc nubs on the asparagine (Asn) residues on the peptide/protein backbone.

The GlcNAc-Asn structures on the peptide/protein backbone is then be modified with galactose or galactose-PEG using UDP-galactose or UDP-galactose-6-PEG, respectively, and a galactosyltransferase such as GalT1. In one case the galactose-PEG is the terminal residue.

In the second case the galactose is further modified with SA-PEG using a CMP-SA-PEG donor and a sialyltransferase such as ST3GalIII. In another embodiment the GlcNAc-Asn structures on the peptide/protein backbone can be galactosylated and sialylated as described above, and then further sialylated using CMP-SA-PEG and an α 2,8-sialyltransferase such as the enzyme encoded by the *Campylobacter jejuni* cst-II gene.

Herceptin™

32. Glycoconjugation of mithramycin to Herceptin™

This example sets forth the procedures to glycoconjugate a small molecule, such as mithramycin to Fc region glycans of an antibody molecule produced in mammalian cells. Here, the antibody Herceptin™ is used, but one of skill in the art will appreciate that the method can be used with many other antibodies.

Preparation of Herceptin™-Gal-linker-mithramycin. Herceptin™ is dissolved at 2.5 mg/mL in 50 mM Tris-HCl, 0.15 M NaCl, 5 mM MnCl₂, 0.05% NaN₃, pH 7.2. The solution is incubated with 1 mM UDP-galactose-linker-mithramycin and 0.1 U/mL of galactosyltransferase at 32°C for 2 days to introduce the mithramycin in the Fc region glycans. To monitor the incorporation of galactose, a small aliquot of the reaction has ¹⁴C-galactose-UDP ligand added; the label incorporated into the peptide is separated from the free label by gel filtration on a Toso Haas G3000SW analytical column using PBS buffer (pH 7.1). The radioactive label incorporation into the peptide is quantitated using an in-line radiation detector.

When the reaction is complete, the reaction mixture is purified using a Toso Haas TSK-Gel-3000 preparative column using PBS buffer (pH 7.1) and collecting fractions based on UV absorption. The fractions containing product are combined, concentrated, buffer exchanged and then freeze-dried. The product of the reaction is analyzed using SDS-PAGE and IEF analysis according to the procedures and reagents supplied by Invitrogen. Samples are dialyzed against water and analyzed by MALDI-TOF MS.

Interferon α and Interferon β 33. GlycoPEGylation of Proteins expressed in Mammalian or Insect Systems:
EPO, Interferon α and Interferon β

This example sets forth the preparation of PEGylated peptides that are expressed in
5 mammalian and insect systems.

Preparation of acceptor from mammalian expression systems. The peptides to be glycoPEGylated using CMP-sialic acid PEG need to have glycans terminating in galactose. Most peptides from mammalian expression systems will have terminal sialic acid that first
needs to be removed.

Sialidase digestion. The peptide is desialylated using a sialidase. A typical
procedure involves incubating a 1 mg/mL solution of the peptide in Tris-buffered saline, pH
7.2, with 5 mM CaCl_2 added, with 0.2 U/mL immobilized sialidase from *Vibrio cholera*
(Calbiochem) at 32°C for 24 hours. Microbial growth can be halted either by sterile filtration
or the inclusion of 0.02% sodium azide. The resin is then removed by centrifugation or
15 filtration, and then washed to recover entrapped peptide. At this point, EDTA may be added
to the solution to inhibit any sialidase that has leached from the resin.

Preparation from insect expression systems. EPO, interferon-alpha, and
interferon-beta may also be expressed in non-mammalian systems such as yeast, plants, or
insect cells. The peptides to be glycoPEGylated using CMP-sialic acid PEG need to have
20 glycans terminating in galactose. The majority of the N-glycans on peptides expressed in
insect cells, for example, are the trimannosyl core. These glycans are first built out to
glycans terminating in galactose before they are acceptors for sialyltransferase.

Building acceptor glycans from trimannosyl core. Peptide (1 mg/mL) in Tris-
buffered saline, pH 7.2, containing 5 mM MnCl_2 , 5 mM UDP-glcNAc, 0.05 U/mL
25 GLCNACT I, 0.05 U/mL GLCNACT II, is incubated at 32°C for 24 hours or until the
reaction is substantially complete. Microbial growth can be halted either by sterile filtration
or the inclusion of 0.02% sodium azide. After buffer exchange to remove UDP and other
small molecules, UDP-galactose and MnCl_2 are each added to 5 mM, galactosyltransferase is
added to 0.05 U/mL, and is incubated at 32°C for 24H or until the reaction is substantially
30 complete. Microbial growth can be halted either by sterile filtration or the inclusion of 0.02%
sodium azide. The peptides are then ready for glycoPEGylation.

Building O-linked glycans. A similar strategy may be employed for interferon alpha to produce enzymatically the desired O-glycan Gal-GalNAc. If necessary, GalNAc linked to serine or threonine can be added to the peptide using appropriate peptide GalNAc transferases (e.g. GalNAc T1, GalNAc T2, T3, T4, etc.) and UDP-GalNAc. Also, if needed, galactose can be added using galactosyltransferase and UDP-galactose.

GlycoPEGylation using sialyltransferase. The glycopeptides (1 mg/mL) bearing terminal galactose in Tris buffered saline + 0.02% sodium azide are incubated with CMP-SA-PEG (0.75 mM) and 0.4 U/mL sialyltransferase (ST3Gal3 or ST3Gal4 for N-glycans on EPO and interferon beta; ST3Gal4, or ST3Gal1 for O-glycans on interferon alpha) at 32°C for 24 hours. Other transferases that may work include the 2,6 sialyltransferase from *Photobacterium damsella*. The acceptor peptide concentration is most preferably in the range of 0.1 mg/mL up to the solubility limit of the peptide. The concentration of CMP-SA-PEG should be sufficient for there to be excess over the available sites, but not so high as to cause peptide solubility problems due to the PEG, and may range from 50 µM up to 5 mM, and the temperature may range from 2°C up to 40°C. The time required for complete reaction will depend on the temperature, the relative amounts of enzyme to acceptor substrate, the donor substrate concentration, and the pH.

34. GlycoPEGylation of Interferon α produced in CHO cells

Preparation of Asialo-Interferon α . Interferon alpha produced from CHO cells is dissolved at 2.5 mg/mL in 50 mM Tris 50 mM Tris-HCl pH 7.4, 0.15 M NaCl, 5 mM CaCl₂ and concentrated to 500 µL in a Centricon Plus 20 centrifugal filter. The solution is incubated with 300 mU/mL Neuraminidase II (*Vibrio cholerae*) for 16 hours at 32 °C. To monitor the reaction a small aliquot of the reaction is diluted with the appropriate buffer and IEF gel performed. The reaction mixture is then added to prewashed N-(p-aminophenyl)oxamic acid-agarose conjugate (800 µL/mL reaction volume) and the washed beads gently rotated for 24 hours at 4 °C. The mixture is centrifuged at 10,000 rpm and the supernatant was collected. The beads are washed 3 times with Tris-EDTA buffer, once with 0.4 mL Tris-EDTA buffer and once with 0.2 mL of the Tris-EDTA buffer and all supernatants were pooled. The supernatant is dialyzed at 4 °C against 50 mM Tris -HCl pH 7.4, 1 M NaCl, 0.05% NaN₃ and then twice more against 50 mM Tris -HCl pH 7.4, 1 M

NaCl, 0.05% NaN₃. The dialyzed solution is then concentrated using a Centricon Plus 20 centrifugal filter and stored at -20 °C. The conditions for the IEF gel are run according to the procedures and reagents provided by Invitrogen. Samples of native and desialylated G-CSF are dialyzed against water and analyzed by MALDI-TOF MS.

5 **Preparation of Interferon-alpha-(alpha2,3)-Sialyl-PEG.** Desialylated interferon-alpha is dissolved at 2.5 mg/mL in 50 mM Tris-HCl, 0.15 M NaCl, 0.05% NaN₃, pH 7.2. The solution is incubated with 1 mM CMP-sialic acid-PEG and 0.1 U/mL of ST3Gal1 at 32°C for 2 days. To monitor the incorporation of sialic acid-PEG, a small aliquot of the reaction had CMP-SA-PEG-fluorescent ligand added; the label incorporated into the peptide
10 is separated from the free label by gel filtration on a Toso Haas G3000SW analytical column using PBS buffer (pH 7.1). The fluorescent label incorporation into the peptide is quantitated using an in-line fluorescent detector. After 2 days, the reaction mixture is purified using a Toso Haas G3000SW preparative column using PBS buffer (pH 7.1) and collecting fractions based on UV absorption. The product of the reaction is analyzed using SDS-PAGE and IEF
15 analysis according to the procedures and reagents supplied by Invitrogen. Samples of native and desialylated Interferon-alpha are dialyzed against water and analyzed by MALDI-TOF MS.

Preparation of Interferon-alpha-(alpha2,8)-Sialyl-PEG. Interferon-alpha produced in CHO, which contains an alpha2,3-sialylated O-linked glycan, is dissolved at 2.5
20 mg/mL in 50 mM Tris-HCl, 0.15 M NaCl, 0.05% NaN₃, pH 7.2. The solution is incubated with 1 mM CMP-sialic acid-PEG and 0.1 U/mL of CST-II at 32°C for 2 days. To monitor the incorporation of sialic acid-PEG, a small aliquot of the reaction has CMP-SA-PEG-fluorescent ligand added; the label incorporated into the peptide is separated from the free label by gel filtration on a Toso Haas G3000SW analytical column using PBS buffer (pH
25 7.1). The fluorescent label incorporation into the peptide is quantitated using an in-line fluorescent detector. After 2 days, the reaction mixture is purified using a Toso Haas G3000SW preparative column using PBS buffer (pH 7.1) and collecting fractions based on UV absorption. The product of the reaction is analyzed using SDS-PAGE and IEF analysis according to the procedures and reagents supplied by Invitrogen. Samples of native and
30 PEGylated interferon-alpha are dialyzed against water and analyzed by MALDI-TOF MS.

Preparation of Interferon-alpha-(alpha2,6)-Sialyl-PEG. Interferon-alpha, containing only O-linked GalNAc, was dissolved at 2.5 mg/mL in 50 mM Tris-HCl, 0.15 M NaCl, 0.05% NaN₃, pH 7.2. The solution is incubated with 1 mM CMP-sialic acid-PEG and 0.1 U/mL of ST6GalNAcI or II at 32°C for 2 days. To monitor the incorporation of sialic acid-PEG, a small aliquot of the reaction had CMP-SA-PEG-fluorescent ligand added; the label incorporated into the peptide is separated from the free label by gel filtration on a Toso Haas G3000SW analytical column using PBS buffer (pH 7.1). The fluorescent label incorporation into the peptide is quantitated using an in-line fluorescent detector. After 2 days, the reaction mixture is purified using a Toso Haas G3000SW preparative column using PBS buffer (pH 7.1) and collecting fractions based on UV absorption. The product of the reaction is analyzed using SDS-PAGE and IEF analysis according to the procedures and reagents supplied by Invitrogen. Samples of native and PEGylated interferon-alpha are dialyzed against water and analyzed by MALDI-TOF MS.

35. GlycoPEGylation of Interferon-β-1a with PEG (10 kDa) and PEG (20 kDa)

This example illustrates a procedure PEGylate Interferon-β with either PEG (10 kDa) or PEG (20 kDa).

Briefly, Interferon-β-1a (INF-β) was obtained from Biogen (Avonex™). The INF-β was first purified by Superdex-75 chromatography. The INF-β was then desialylated with *Vibrio cholerae* sialidase. The INF-β was then PEGylated with SA-PEG (10 kDa) or SA-PEG (20 kDa) and purified with Superdex-200 chromatography.

Superdex-75 chromatography purification. INF-β (150 μg) was applied to a Superdex-75 column (Amersham Biosciences, Arlington Heights, IL) and eluted with PBS with 0.5 M NaCl, 0.02 Tween-20, 20 mM histidine and 10% glycerol. The eluant was monitored for absorbance at 280 nm (Figure 172A and 172B) and fractions were collected. Peaks 4 and 5 were pooled, concentrated in an Amicon Ultra 15 spin filter (Millipore, Billerica, MA), and the buffer was exchanged to TBS with 5 mM CaCl₂, 0.02% Tween-20, 20 mM histidine and 10% glycerol.

Sialidase Reaction. The INF-β was then desialylated with *Vibrio cholera* sialidase (70 mU/ml, CALBIOCHEM®, EMD Biosciences, Inc., San Diego, CA) on agarose in TBS

with 5 mM CaCl_2 , 0.02% Tween-20, 20 mM histidine and 10% glycerol. The reaction was carried out at 32°C for 18 hours. The INF- β was removed from the agarose with a 0.22 μm Spin-X™ filter (Corning Technology, Inc., Norcross, GA). Figure 173A depicts the MALDI analysis of glycans released from native INF- β . The native INF- β has many glycoforms containing terminal sialic acid moieties. Figure 173B depicts the MALDI analysis of glycans released from desialylated INF- β . The desialylated INF- β has primarily one glycoform which is bi-antennary with terminal galactose moieties.

Lectin Dot-Blot Analysis of Sialylation. Samples of the INF- β from the desialidase reaction were dot-blotted onto nitrocellulose and then blocked with Tris buffered saline (TBS: 0.05M Tris, 0.15M NaCl, pH 7.5) and DIG kit (glycan differentiation kit available from Roche #1 210 238) blocking buffer. Some of the blots were incubated with *Maackia amurensis* agglutinin (MAA) labeled with digoxigenin (DIG) (Roche Applied Science, Indianapolis, IL) to detect α 2,3-sialylation of INF- β . These blots were washed with TBS then incubated with anti-digoxigenin antibody labeled with alkaline phosphatase, then washed again with TBS and developed with NBT/X-phosphate solution, wherein NBT is 4-nitro blue tetrazolium chloride and X-phosphate is 5-bromo-4-chloro-3-indoyl phosphate. The left side of Figure 174 depicts the results of the MAA blot of INF- β after the desialylation reaction. The INF- β is partially desialylated, as indicated by the decrease in dot development as compared to native INF- β in the desialylated samples.

Other blots were incubated with *Erthrina cristagalli* lectin (ECL) labeled with biotin (Vector Laboratories, Burlingame, CA) to detect exposed galactose residues on INF- β . After incubation with 2.5 $\mu\text{g/ml}$ ECL, the blots were washed in TBS and incubated with streptavidin labeled with alkaline phosphatase. The blots were then washed again and developed. The right side of Figure 174 depicts the ECL blot after development. The increased intensity of the dot of desialylated INF- β as compared to the native INF- β indicate more exposed galactose moieties and therefore extensive desialylation.

PEGylation of Desialylated INF- β with SA-PEG (10 kDa). Desialylated INF- β (0.05 mg/ml) was PEGylated with ST3Gal3 (50 mU/ml) and CMP-SA-PEG (10 kDa) (250 μM) in an appropriate buffer of TBS + 5 mM CaCl_2 , 0.02% Tween 20, 20 mM histidine, 10%

glycerol for 50 hours at 32°C. Figure 175 depicts the SDS-PAGE analysis of the reaction products showing PEGylated INF- β at approximately 98 kDa.

PEGylation of Desialylated INF- β with SA-PEG (20 kDa). Desialylated INF- β (0.5 mg/ml) was PEGylated with ST3Gal3 (170 mU/ml) and CMP-SA-PEG (20 kDa) in an appropriate buffer of TBS + 5 mM CaCl₂, 0.02% Tween 20, 20 mM histidine, 10% glycerol for 50 hours at 32°C. Figure 176 depicts the SDS-PAGE analysis the products of the PEGylation reaction. The PEGylated INF- β has many higher molecular weight bands not found in the unmodified INF- β indicating extensive PEGylation.

Superdex-200 Purification of INF- β PEGylated with PEG (10 kDa). The products of the PEGylation reaction were separated on a Superdex-200 column (Amersham Biosciences, Arlington Heights, IL) in PBS with 0.5 NaCl, 0.02 Tween-20, 20 mM histidine and 10% glycerol at 1ml/min and 30 cm/hr flow. The eluant was monitored for absorbance at 280 nm (Figure 177) and fractions were collected. Peaks 3 and 4 were pooled and concentrated in an Amicon Ultra 15 spin filter.

Bioassay of INF- β PEGylated with PEG (10 kDa).

The test is inhibition of the proliferation of the lung carcinoma cell line, A549. The A549 cell line are lung carcinoma adherent cells growing in RPMI + 10% FBS at 37°C 5% CO₂. They can be obtained from ATCC # CCL-185. Wash the cells with 10 ml of PBS and remove the PBS. Add 5 ml of trypsin, incubate for 5 minutes at room temperature or 2 minutes at 37°C. When the cells are detached resuspend into 25 ml of media and count the cells. Dilute the cells at a concentration of 10000 cells/ml and add 200 μ l / well (96 wells plate). Incubate for 4 hours at 37°C 5% CO₂. Prepare 1 ml of IFN β at a concentration of 0.1 μ g/ml. Filter it under the hood with a 0.2 μ m filter. Add 100 μ l per well (8 replicates = 1 lane). Incubate for 3 days (do not let the cells go to confluence). Remove 200 μ l of media (only 100 μ l per well left). Add 25 μ l of MTT (Sigma) (5 mg/ml filtered 0.22 μ m). Incubate for 4 hours at 37°C and 5% CO₂. Aspirate the media gently and add 100 μ l of a mixture of isopropanol (100 ml and 6N HCl. Aspirate up and down to homogenize the crystal violet. Read OD 570nm (remove the background at 630 or 690 nm).

Figure 178 depicts the results of the bioassay of the peaks containing INF- β PEGylated with PEG (10 kDa) as eluted from the Superdex-200 column.

Superdex-200 Purification of INF- β PEGylated with PEG (20 kDa). The products of the PEG (20 kDa) PEGylation reaction were separated on a Superdex-200 column (Amersham Biosciences, Arlington Heights, IL) in PBS with 0.5 NaCl, 0.02 Tween-20, 20 mM histidine and 10% glycerol at 1 ml/min flow. The eluant was monitored for absorbance at 280 nm (Figure 179) and fractions were collected. Peak 3 contained most of the INF- β PEGylated with PEG (20 kDa).

Endotoxin test of INF- β PEGylated with PEG (20 kDa).

Limulus Lysate Test was performed, BioWhittaker # 50-647U

Table 24. Results of the endotoxin test of INF- β PEGylated with PEG (20 kDa).

	Concentration		
INF- β with PEG (20 kDa)	10 EU/ml	0.06 mg/ml	0.16 EU/ μ g
INF- β with PEG (20 kDa)	1 EU/ml	0.07 mg/ml	0.014 EU/ μ g
Native INF- β	40 EU/ml	0.1 mg/ml	0.4 EU/ μ g

Remicade™

36. GlycoPEGylation of Remicade™ antibody

This example sets forth the procedure to glycoPEGylate a recombinant antibody molecule by introducing PEG molecules to the Fc region glycans. Here Remicade™, a TNF-R: IgG Fc region fusion protein, is the exemplary peptide.

Preparation of Remicade™-Gal-PEG (10 kDa). Remicade™ is dissolved at 2.5 mg/mL in 50 mM Tris-HCl, 0.15 M NaCl, 5 mM MnCl₂, 0.05% NaN₃, pH 7.2. The solution is incubated with 1 mM UDP-galactose-PEG (10 kDa) and 0.1 U/mL of galactosyltransferase at 32°C for 2 days to introduce the PEG in the Fc region glycans. To monitor the incorporation of galactose, a small aliquot of the reaction has ¹⁴C-galactose-UDP ligand added; the label incorporated into the peptide is separated from the free label by gel filtration on a Toso Haas G3000SW analytical column using PBS buffer (pH 7.1). The radioactive label incorporation into the peptide is quantitated using an in-line radiation detector.

When the reaction is complete, the reaction mixture is purified using a Toso Haas TSK-Gel-3000 preparative column using PBS buffer (pH 7.1) and collecting fractions based on UV absorption. The fractions containing product are combined, concentrated, buffer

exchanged and then freeze-dried. The product of the reaction is analyzed using SDS-PAGE and IEF analysis according to the procedures and reagents supplied by Invitrogen. Samples are dialyzed against water and analyzed by MALDI-TOF MS.

Rituxan™

37. Glycoconjugation of geldanamycin to Rituxan™

This example sets forth the glycoconjugation of a small molecule, such as geldanamycin, to the Fc region glycans of an antibody produced in CHO cells, such as Rituxan™. Here, the antibody Rituxan™ is used, but one of skill in the art will appreciate that the method can be used with many other antibodies.

Preparation of Rituxan™-Gal-linker-geldanamycin. Rituxan™ is dissolved at 2.5 mg/mL in 50 mM Tris-HCl, 0.15 M NaCl, 5 mM MnCl₂, 0.05% NaN₃, pH 7.2. The solution is incubated with 1 mM UDP-galactose-linker-geldanamycin and 0.1 U/mL of galactosyltransferase at 32°C for 2 days to introduce the geldanamycin in the Fc region glycans. To monitor the incorporation of galactose, a small aliquot of the reaction has ¹⁴C-galactose-UDP ligand added; the label incorporated into the peptide is separated from the free label by gel filtration on a Toso Haas G3000SW analytical column using PBS buffer (pH 7.1). The radioactive label incorporation into the peptide is quantitated using an in-line radiation detector.

When the reaction is complete, the reaction mixture is purified using a Toso Haas TSK-Gel-3000 preparative column using PBS buffer (pH 7.1) and collecting fractions based on UV absorption. The fractions containing product are combined, concentrated, buffer exchanged and then freeze-dried. The product of the reaction is analyzed using SDS-PAGE and IEF analysis according to the procedures and reagents supplied by Invitrogen. Samples are dialyzed against water and analyzed by MALDI-TOF MS.

Rnase

38. Remodeling high mannose N-glycans to hybrid and complex N-glycans: Bovine pancreatic RNase

This example sets forth the preparation of bovine pancreas RNase with hybrid or complex N-glycans. The high mannose N-linked glycans of the RNase are enzymatically

digested and elaborated to create hybrid N-linked glycans. Additionally, the high mannose N-linked glycans of the RNase are enzymatically digested and elaborated to create complex N-linked glycans.

High mannose structures of N-linked oligosaccharides in glycopeptides can be modified to hybrid or complex forms using the combination of α -mannosidases and glycosyltransferases. This example summarizes the results in such efforts using a simple N-Glycan as a model substrate.

Ribonuclease B (RNaseB) purified from bovine pancreas (Sigma) is a glycopeptide consisting of 124 amino acid residues. It has a single potential N-glycosylation site modified with high mannose structures. Due to its simplicity and low molecular weight (13.7 kDa to 15.5 kDa), ribonuclease B is a good candidate to demonstrate the feasibility of the N-Glycan remodeling from high mannose structures to hybrid or complex N-linked oligosaccharides. The MALDI-TOF spectrum of RNaseB (Figure 180A) and HPLC profile for the oligosaccharides cleaved from RNaseB by N-Glycanase (Figure 180B) indicated that, other than a small portion of the non-modified peptide, the majority of N-glycosylation sites of the peptide are modified with high mannose oligosaccharides consisting of 5 to 9 mannose residues.

Conversion of high mannose N-Glycans to hybrid N-Glycans. High mannose N-Glycans were converted to hybrid N-Glycans using the combination of α 1,2-mannosidase, GlcNAcT-I (β -1,2-N-acetyl glucosaminyl transferase), GalT-I (β 1,4-galactosyltransferase) and α 2,3-sialyltransferase /or α 2,6-sialyltransferase as shown in Figure 181.

As an example, high mannose structures in RNaseB were successfully converted to hybrid structures.

Man₅GlcNAc₂-R was obtained from Man₅₋₉GlcNAc₂-R catalyzed by a single α 1,2-mannosidase cloned from *Trichoderma reesei* (Figure 182). RNase B (1 g, about 67 μ mol) was incubated at 30°C for 45 hr with 15 mU of the recombinant *T. reesei* α 1,2-mannosidase in MBS buffer (50 mM, pH 6.5) in a total volume of 10 mL. Man₅₋₉GlcNAc₂-protein structures have been successfully converted to Man₅GlcNAc₂-protein with high efficiency by the recombinant mannosidase.

Alternately, $\text{Man}_5\text{GlcNAc}_2\text{-R}$ was obtained from $\text{Man}_5\text{-}_9\text{GlcNAc}_2\text{-R}$ catalyzed by a single $\alpha 1,2$ -mannosidase purified from *Aspergillus saitoi* (Figure 183). RNase B (40 μg , about 2.7 nmol) was incubated at 37°C for 42.5 hr with 25 μU of the commercial *A. saitoi* $\alpha 1,2$ -mannosidase (Glyko or CalBioChem) in NaOAc buffer (100 mM, pH 5.0) in a total volume of 20 μL . $\text{Man}_5\text{-}_9\text{GlcNAc}_2$ -protein structures were successfully converted to $\text{Man}_5\text{GlcNAc}_2$ -protein by the commercially available mannosidase. However, a new peak corresponding to the GlcNAc-protein appears in the spectrum, indicating the possible contamination of endoglycosidase H in the preparation. Although several mammalian α -mannosidases were required to achieve this step, the fungal $\alpha 1,2$ -mannosidase was very efficient to remove all $\alpha 1,2$ -linked mannose residues.

GlcNAcT-I then added a GlcNAc residue to the $\text{Man}_5\text{GlcNAc}_2\text{-R}$ (Figure 184). The reaction mixture after the *T. reesei* $\alpha 1,2$ -mannosidase reaction containing RNase B (600 μg , about 40 nmol) was incubated with non-purified recombinant GlcNAcT-I (34 mU) in MES buffer (50 mM, pH 6.5) containing MnCl_2 (20 mM) and UDP-GlcNAc (5 mM) in a total volume of 400 μL at 37°C for 42 hr. A GlcNAc residue was quantitatively added to $\text{Man}_5\text{GlcNAc}_2$ -protein by the recombinant GlcNAcT-I.

A Gal residue was then added using GalT 1 (Figure 185). The reaction mixture after the GnT-I reaction containing RNase B (120 μg , about 8 nmol) was incubated at 37°C for 20 hr with 3.3 mU of the recombinant GalT-1 in Tris-HCl buffer (100 mM, pH 7.3) containing UDP-Gal (7.5 mM) and MnCl_2 (20 mM) in a total volume of 100 μL . A Gal residue was added to about 98% of the GlcNAc- $\text{Man}_5\text{GlcNAc}_2$ -protein by the recombinant GalT 1.

The next step was the addition of a sialic acid using an $\alpha 2,3$ -sialyltransferase or an $\alpha 2,6$ -sialyltransferase (Figure 186). As an example, ST3Gal III, an $\alpha 2,3$ -sialyltransferase was used. The reaction mixture after the GalT-1 reaction containing RNase B (13 μg , about 0.87 nmol) was incubated at 37°C for 16 hr with 8.9 mU of recombinant ST3Gal III in Tris-HCl buffer (100 mM, pH 7.3) containing CMP-Sialic acid (5 mM) and MnCl_2 (20 mM) in a total volume of 20 μL . A sialic acid residue was added to about 90% of the Gal-GlcNAc- $\text{Man}_5\text{GlcNAc}_2$ -protein by recombinant ST3Gal III using CMP-SA as the donor. The yield can be further improved by adjusting the reaction conditions.

For convenience, no purification or dialysis step was required after each reaction described above. More interesting, GalT 1 and ST3Gal III can be combined in a one-pot reaction. Similar yields were obtained as compared with the separate reactions. The reaction mixture after the GlcNAcT-I reaction containing RNase B (60 μ g, about 4 nmol) was
5 incubated at 37°C for 20 hr with 1.7 mU of recombinant GalT 1, 9.8 mU of recombinant ST3Gal III in Tris-HCl buffer (100 mM, pH 7.3) containing UDP-Gal (7.5 mM), CMP-sialic acid (5 mM) and MnCl₂ (20 mM) in a total volume of 60 μ l.

As shown in Figure 187, SA-PEG (10 kDa) was successfully added to the RNaseB. The reaction mixture after the GalT-1 reaction containing RNase B (6.7 μ g, about 0.45 nmol)
10 was dialyzed against H₂O for 1 hour at room temperature and incubated at 37°C for 15.5 hours with 55 mU of the recombinant ST3Gal III in Tris-HCl buffer (50 mM, pH 7.3) containing CMP-SA-PEG (10 kDa) (0.25 mM) and MnCl₂ (20 mM) in a total volume of 20 μ l. PEG-modified sialic acid residues were successfully added to the Gal-GlcNAc-Man₅GlcNAc₂-peptide by the recombinant ST3Gal III. The yield can be further improved by
15 adjusting the reaction conditions.

Conversion of high mannose N-Glycans to complex N-Glycans. To achieve this conversion, a GlcNAc β 1,2Man₃GlcNAc₂-peptide intermediate is obtained. As shown in Figure 188, there are at least four feasible routes to carry out the reaction from Man₅GlcNAc₂-peptide to this intermediate:

Route I: The Man₅GlcNAc₂-peptide produced by the fungal α 1,2 mannosidase is a substrate of GlcNAc transferase I (GlcNAcT-I, enzyme 2) which adds one GlcNAc. The terminal α 1,3- and α 1,6-linked mannose residues of GlcNAcMan₅GlcNAc₂-peptide is removed by Golgi α -mannosidase II (ManII, enzyme 5). This route is a part of the natural pathway for the processing of N-linked oligosaccharides carried out in higher organisms.

Route II: Two mannose residues are first removed by an α -mannosidase (enzyme 6), then a GlcNAc is added by GlcNAcT-I (enzyme 2). Other than its natural acceptor Man₅GlcNAc₂-R, GlcNAcT-I can also recognize Man₃GlcNAc₂-R as its substrate and add one GlcNAc to the mannose core structure to form GlcNAcMan₃GlcNAc₂-peptide.

Route III: The α 1,6-linked mannose is removed by an α 1,6-mannosidase, followed
30 by the addition of GlcNAc by GlcNAcT-I and removal of the terminal α 1,3-linked mannose

by an α 1,3-mannosidase. From the experimental data obtained, GlcNAcT-I can recognize this Man₄GlcNAc₂-peptide as acceptor and add one GlcNAc residue to form GlcNAcMan₄GlcNAc₂-peptide.

Route IV: Similar to Route III, α 1,3-linked mannose is removed by an α 1,3-mannosidase, followed by GlcNAcT-I reaction. Then the terminal α 1,6-linked mannose can be removed by an α 1,6-mannosidase.

After the function of GlcNAcT-I (responsible for the addition of the GlcNAc β 1,2-linked to the α 1,3-mannose on the mannose core) and GlcNAcT-II (responsible for the addition of a second GlcNAc β 1,2-linked to the α 1,6-mannose on the mannose core), the GlcNAc₂Man₃GlcNAc₂-peptide can be processed by GalT 1 and sialyltransferase to form bi-antennary complex N- Glycans. Other GlcNAc transferases such as GlcNAcT-IV, GlcNAcT-V, and/or GlcNAcT-VI (Figure 188 and Figure 189) can also glycosylate the GlcNAc₂Man₃GlcNAc₂-peptide. Additional glycosylation by the GalT 1 and sialyltransferases will form multi-antennary complex N-glycans. The enzyme GlcNAcT-III catalyzes the insertion of a bisecting GlcNAc, thus preventing the actions of ManII and subsequent action of transferases GlcNAcT-II, GlcNAcT-IV and GlcNAcT-V.

Tissue-Type Plasminogen Activator (TPA)

39. Fucosylation of TPA to create Sialyl Lewis X

This example sets forth the preparation of Tissue Type Plasminogen Activator (TPA) with N-linked sialyl Lewis X antigen.

Sialylation. TPA expressed in mammalian cells will often contain a majority of the glycans terminating in sialic acid, but to ensure complete sialylation, it would be beneficial to first perform an *in vitro* sialylation. TPA in a suitable buffer (most preferably between pH 5.5 and 9, for example Tris buffered saline, pH 7.2) is incubated with CMP sialic acid and sialyltransferase for a time sufficient to convert any glycans lacking sialic acid to sialylated species. Typical conditions would be 1 mg/mL TPA, 3 mM CMP sialic acid, 0.02 U/mL ST3Gal3, 32°C for 24 hours. Microbial growth can be halted either by sterile filtration or the inclusion of 0.02% sodium azide. The TPA concentration is most preferably in the range 0.1 mg/mL up to the solubility limit of the peptide. The concentration of CMP-SA should be

sufficient for there to be excess over the available sites, and might range from 50 μ M up to 50 mM, and the temperature from 2°C up to 40°C. The time required for complete reaction will depend on the temperature, the relative amounts of enzyme to acceptor substrate, the donor substrate concentration, and the pH. Other sialyltransferases that may be capable of adding sialic acid in 2,3 linkage include ST3Gal4; microbial transferases could also be used.

Fucosylation. Typical conditions for fucosylation would be 1 mg/mL TPA, 3 mM GDP-fucose, 0.02 U/mL FTVI, 5 mM $MnCl_2$, 32°C for 24H in Tris buffered saline. Microbial growth can be halted either by sterile filtration or the inclusion of 0.02% sodium azide. The TPA concentration is most preferably in the range 0.1 mg/mL up to the solubility limit of the peptide. The concentration of GDP-fucose should be sufficient for there to be excess over the available sites, and might range from 50 μ M up to 50 mM, and the temperature from 2°C up to 40°C. The time required for complete reaction will depend on the temperature, the relative amounts of enzyme to acceptor substrate, the donor substrate concentration, and the pH. Other fucosyltransferases that may be capable of making sialyl Lewis x include FTVII, FTV, FTIII, as well as microbial transferases could also be used.

40. Trimming of high mannose to tri-mannose core structure: Tissue-type Plasminogen Activator produced in CHO

This example sets forth the preparation of Tissue-type Plasminogen Activator with a trimannose core by trimming back from a high mannose glycan.

Tissue-type plasminogen activator (TPA) is currently produced in Chinese Hamster Ovary (CHO) cells and contains a low amount of high mannose N-linked oligosaccharide. The mannoses can be trimmed down using a variety of the specific mannosidases. The first step is to generate Man5GlcNAc2(Fuc0-1) from Man9GlcNAc2(Fuc0-1). This can be done using mannosidase I. Then either GlcNAcT1 (GlcNAc transferase I) is used to make GlcNAc1Man5GlcNAc2(Fuc0-1) or Mannosidase III is used to make Man3GlcNAc2(Fuc0-1). From Man3GlcNAc2(Fuc0-1), GlcNAc1Man3GlcNAc2(Fuc0-1) can be produced using GlcNAcT1 or from GlcNAc1Man5GlcNAc2(Fuc0-1), GlcNAc1Man3GlcNAc2(Fuc0-1) can be produced using Mannosidase II. GlcNAc1Man3GlcNAc2(Fuc0-1) is then converted into GlcNAc2Man3GlcNAc2(Fuc0-1) using GlcNAcTransferase II (GlcNAcTII). The two

terminal GlcNAc residues are then galactosylated using GalTI and then sialylated with SA-PEG using ST3GalIII.

Conversely, TPA can be produce in yeast or fungal systems. Similar processing would be required for fungal derived material.

41. Generation and PEGylation of GlcNAc-Asn structures: TPA produced in Yeast

This example sets forth the preparation of PEGylated GlcNAc-Asn structures on a peptide such as TPA expressed in yeast.

Yeast expression is expected to result in a TPA which contains a single N-linked mannan-type structure. This recombinant glycoprotein is first treated with endoglycosidase H to generate GlcNAc structures on the asparagine (Asn) residues on the peptide.

The GlcNAc-Asn structures on the peptide/protein backbone are then be modified with galactose or galactose-PEG using UDP-galactose or UDP-galactose-6-PEG, respectively, and a galactosyltransferase such as GalT1. In one case, the galactose-PEG is the terminal residue. In the second case, the galactose is further modified with SA-PEG using a CMP-SA-PEG donor and a sialyltransferase such as ST3GalIII. In another embodiment, the GlcNAc-Asn structures on the peptide/protein backbone may be galactosylated and sialylated as described above, and then further sialylated using CMP-SA-PEG and an α 2,8-sialyltransferase such as the enzyme encoded by the *Campylobacter jejuni* cst-II gene.

Transferrin

42. GlycoPEGylation of Transferrin

This example sets forth the preparation of asialotransferrin and its sialylation with PEG-CMP-sialic acid.

Preparation of Asialo-transferrin. Human-derived holo-Transferrin, (10 mg) was dissolved in 500 μ L of 50 mM NaOAc, 5 mM CaCl_2 , pH 5.5. To this solution was added 500 mU Neuraminidase II (*Vibrio cholerae*) and the reaction mixture was shaken gently for 20.5 hours at 37 °C. The reaction mixture was added to the prewashed N-(p-aminophenyl)oxamic acid-agarose conjugate (600 μ L) and the washed beads gently rotated

for 24 hours at 4 °C. The mixture was centrifuged at 10,000 rpm and the supernatant was collected. The reaction mixture was adjusted to 5 mM EDTA by addition of 100 µL of 30 mM EDTA to the washed beads, which were gently rotated for 20 hours at 4 °C. The suspension was centrifuged for 2 minutes at 10,000 rpm and the supernatant was collected.

5 The beads were washed 5 times with 0.35 mL of 50 mM NaOAc, 5 mM CaCl₂, 5 mM EDTA, pH 5.5 and all supernatants were pooled. The enzyme solution was dialyzed twice at 4 °C into 15 mM Tris-HCl, 1 M NaCl, pH 7.4. 0.3 mL of the transferrin solution (3.3 mL total) was removed and dialyzed twice against water. The remainder was dialyzed twice more at 4 °C against phosphate buffered saline. The dialyzed solution was stored at -20 °C.

10 Protein samples were analyzed by IEF Electrophoresis. Samples (9 µL, 25 µg) were diluted with 16 µL Tris buffer and mixed with 25 µL of the sample loading buffer and applied to Isoelectric Focusing Gels (pH 3-7). Gels were run and fixed using standard procedures. Gels were stained with Colloidal Blue Stain.

Sialyl-PEGylation of asialo-Transferrin. Desialylated transferrin (250 µg) and
15 CMP-sialic acid or CMP-SA-PEG (1 kDa or 10 kDa)(0.05 µmol) were dissolved in 69 µL 50 mM Tris-HCl, 0.15 M NaCl, 0.05% NaN₃, pH 7.2 in 1.5 mL plastic tubes. The tubes were vortexed briefly and 100 mU ST3Gal3 (90 µL) were added (total volume 250 µL). The tubes were vortexed again and mixed gently for 24 hours at 32 °C. The reactions were stopped by freezing at -80 °C. Novex Tris-Glycine 8-16% 1 mm gels were used for SDS
20 PAGE analysis (Figure 190). Samples (25 µL, 25 µg) were mixed with 25 µL of sample loading buffer and 0.4 µL of β-mercaptoethanol and heated for 6 minutes at 85 °C. Gels were run using standard conditions and stained with Colloidal Blue Stain. IEF gels were also performed as described above (Figure 191). Samples were also dialyzed against water analyzed by MALDI-TOF.

25 **Results.** MALDI was also performed. Native transferrin (78729); asialotransferrin (78197); resialylated transferrin (79626/80703); with SA-PEG 1k (79037 (1); 80961 (2); 82535 (3); 84778 (4)); with SA-PEG 5k (90003 (2); 96117 (3); 96117 (4)); with SA-PEG 10k (100336 (2); 111421 (3); 122510 (4)).

43. Transferrin-GDNF

This example sets forth the procedures for the glycoconjugation of proteins, and in particular, transferrin is glycoconjugated to GDNF. Transferrin-SA-Linker-Gal-UDP is prepared from transferrin. The galactose residue is removed from GDNF glycans, and

5 Transferrin-SA-Linker-Gal-UDP is conjugated to GDNF glycans using a galactosyltransferase.

Preparation of agalacto-GDNF. GDNF produced in NSO cells (NSO murine myeloma cells) is dissolved at 2.5 mg/mL in 50 mM Tris 50 mM Tris-HCl pH 7.4, 0.15 M NaCl, and is incubated with 300 mU/mL beta-galactosidase-agarose conjugate for 16 hours at
10 32°C. To monitor the reaction a small aliquot of the reaction is diluted with the appropriate buffer and a IEF gel performed according to Invitrogen procedures. The mixture is centrifuged at 10,000 rpm and the supernatant is collected. The supernatant is dialyzed at 4 °C against 50 mM Tris -HCl pH 7.4, 1 M NaCl, 0.05% NaN₃ and then twice more against 50 mM Tris -HCl pH 7.4, 1 M NaCl, 0.05% NaN₃. The dialyzed solution is then concentrated
15 using a Centricon Plus 20 centrifugal filter and stored at -20 °C. The conditions for the IEF gel are run according to the procedures and reagents provided by Invitrogen. Samples are dialyzed against water and analyzed by MALDI-TOF MS.

Preparation of Transferrin-SA-Linker-Gal-UDP. Asialo-transferrin is dissolved at 2.5 mg/mL in 50 mM Tris-HCl, 0.15 M NaCl, 0.05% NaN₃, pH 7.2. The solution is
20 incubated with CMP-sialic acid-linker-Gal-UDP (molar amount to add 1 molar equivalent of nucleotide sugar to transferrin) and 0.1 U/mL of ST3Gal3 at 32°C for 2 days. To monitor the incorporation of sialic acid, a small aliquot of the reaction has ¹⁴C-SA-UDP ligand added; the label incorporated into the peptide is separated from the free label by gel filtration on a Toso Haas G3000SW analytical column using PBS buffer (pH 7.1). The radioactive label
25 incorporation into the peptide is quantitated using an in-line radiation detector.

The solution is incubated with 5 mM CMP-sialic acid and 0.1 U/mL of ST3Gal3 (to cap any unreacted transferrin glycans) at 32°C for 2 days. The incorporation into the peptide is quantitated using an in-line UV detector. After 2 days, the reaction mixture is purified using a Toso Haas G3000SW preparative column using PBS buffer (pH 7.1) and collecting
30 fractions based on UV absorption. The product of the reaction is analyzed using SDS-PAGE

and IEF analysis according to the procedures and reagents supplied by Invitrogen. Samples are dialyzed against water and analyzed by MALDI-TOF MS.

Preparation of Transferrin-SA-Linker-Gal-GDNF. The transferrin-SA-Linker-Gal-UDP prepared as described above is dissolved at 2.5 mg/mL in 50 mM Tris-HCl, 0.15 M NaCl, 5 mM MnCl₂, 0.05% NaN₃, pH 7.2. The solution is incubated with 2.5 mg/mL agalacto-GDNF and 0.1 U/mL of galactosyltransferase at 32°C for 2 days. To monitor the incorporation of galactose, a small aliquot of the reaction has ¹⁴C-galactose-UDP ligand added; the label incorporated into the peptide is separated from the free label by gel filtration on a Toso Haas G3000SW analytical column using PBS buffer (pH 7.1). The radioactive label incorporation into the peptide is quantitated using an in-line radiation detector.

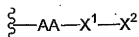
When the reaction is complete, the solution is incubated with 5 mM UDP-Gal and 0.1 U/mL of galactosyltransferase (to cap any unreacted transferrin glycans) at 32°C for 2 days followed by addition of 5 mM CMP-SA and 0.1 U/mL of ST3Gal3. After 2 additional days, the reaction mixture is purified using a Toso Haas G3000SW preparative column using PBS buffer (pH 7.1) collecting fractions based on UV absorption. The product of the reaction is analyzed using SDS-PAGE and IEF analysis according to the procedures and reagents supplied by Invitrogen. Samples are dialyzed against water and analyzed by MALDI-TOF MS.

The disclosures of each and every patent, patent application, and publication cited herein are hereby incorporated herein by reference in their entirety.

While this invention has been disclosed with reference to specific embodiments, it is apparent that other embodiments and variations of this invention may be devised by others skilled in the art without departing from the true spirit and scope of the invention. The appended claims are intended to be construed to include all such embodiments and equivalent variations.

What is claimed:

1. A cell-free, in vitro method of remodeling a peptide comprising poly(ethylene glycol), the peptide having the formula:



wherein

AA is a terminal or internal amino acid residue of the peptide;

X¹-X² is a saccharide covalently linked to the AA, wherein

X¹ is a first glycosyl residue; and

X² is a second glycosyl residue covalently linked to X¹, wherein X¹ and X² are

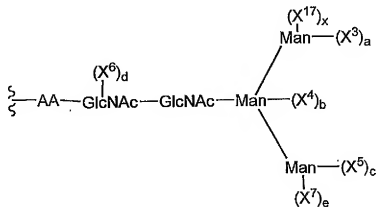
selected from monosaccharyl and oligosaccharyl residues;

the method comprising:

(a) removing X² or a saccharyl subunit thereof from the peptide, thereby forming a truncated glycan.

2. The method according to claim 1 wherein said truncated glycan is formed by removing a Sia residue.

3. The method according to claim 1 wherein said peptide has the formula:



wherein

X^3 , X^4 , X^5 , X^6 , X^7 , and X^{17} , are independently selected monosaccharyl or oligosaccharyl residues; and

a, b, c, d, e, and x are independently selected from the integers 0, 1 and 2.

- 5 4. The method according to claim 3 wherein said oligosaccharyl residue is a member selected from GlcNAc-Gal-Sia and GlcNAc-Gal.
5. The method according to claim 3 wherein at least one member selected from a, b, c, d, e and x is 1 or 2.
- 10 6. The method of claim 3, wherein said removing of step (a) produces a truncated glycan in which at least one of a, b, c, e and x are 0.
7. The method of claim 6, wherein X^3 , X^5 and X^7 are members independently selected from (mannose)_z and (mannose)_z-(X^8)
- 15 wherein

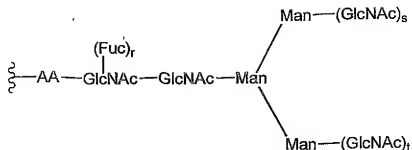
X^8 is a glycosyl moiety selected from mono- and oligo-saccharides; and z is an integer between 1 and 20, wherein

- 20 when z is 3 or greater, each (mannose)_z is independently selected from linear and branched structures.

8. The method of claim 6 wherein X^4 is selected from the group consisting of GlcNAc and xylose.

- 25 9. The method of claim 6, wherein X^3 , X^5 and X^7 are (mannose)_u wherein u is selected from the integers between 1 and 20, and when u is 3 or greater, each (mannose)_u is independently selected from linear and branched structures.

- 30 10. The method according to claim 3 wherein said peptide has the formula:

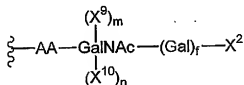


wherein

r, s, and t are integers independently selected from 0 and 1.

5

11. The method of claim 1, wherein said peptide has the formula:



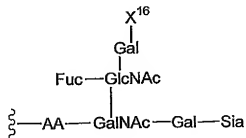
wherein

X^9 and X^{10} are independently selected monosaccharyl or oligosaccharyl

10 residues; and

m, n and f are integers independently selected from 0 and 1.

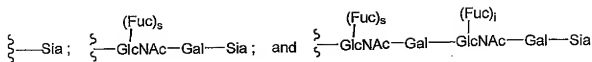
12. The method of claim 11, wherein said peptide has the formula:



15

wherein

X^{16} is a member selected from:

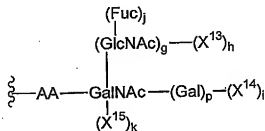


wherein

s and i are integers independently selected from 0 and 1.

5

13. The method of claim 12, wherein said peptide has the formula:



wherein

X^{13} , X^{14} , and X^{15} are independently selected glycosyl residues; and
g, h, i, j, k, and p are independently selected from the integers 0 and 1

10

14. The method according to claim 13 wherein at least one of g, h, i, j, k
and p is 1.

15

15. The method of claim 13, wherein

X^{14} and X^{15} are members independently selected from GlcNAc and Sia; and
i and k are independently selected from the integers 0 and 1.

20

16. The method according to claim 15 wherein at least one of i and k is 1,
and if k is 1, g, h, and j are 0.

17. The method according to claim 1, further comprising:

(b) contacting the truncated glycan with at least one glycosyltransferase
and at least one glycosyl donor under conditions suitable to transfer the at least one glycosyl

donor to the truncated glycan, thereby remodeling said peptide comprising poly(ethylene glycol).

18. The method according to claim 17 wherein said glycosyl donor
5 comprises a modifying group covalently linked thereto.

19. The method of claim 1, further comprising:

(c) removing X^1 , thereby exposing AA.

10 20. The method according to claim 19, further comprising:
(d) contacting AA with at least one glycosyltransferase and at least one
glycosyl donor under conditions suitable to transfer said at least one glycosyl donor to AA,
thereby remodeling said peptide comprising poly(ethylene glycol).

15 21. The method according to claim 20 wherein said at least one glycosyl
donor comprises a modifying group covalently linked thereto.

22. The method according to claim 21 wherein said modifying group is
poly(ethylene glycol).

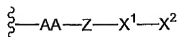
20 23. The method according to claim 22 wherein said poly(ethylene glycol)
has a molecular weight distribution that is essentially homodisperse.

24. The method of claim 17, further comprising:

25 (e) prior to step (b), removing a group added to said saccharide during
post-translational modification.

25. The method of claim 24 wherein said group is a member selected from
phosphate, sulfate, carboxylate and esters thereof.

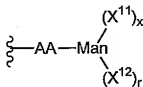
30 26. The method of claim 1 wherein said peptide has the formula:



wherein

Z is a member selected from O, S, NH and a cross-linker.

- 5 27. The method of claim 1, wherein said peptide has the formula:



wherein

X^{11} and X^{12} are independently selected glycosyl moieties; and

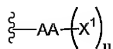
r and x are integers independently selected from 0 and 1.

10

28. The method of claim 27, wherein X^{11} and X^{12} are (mannose)_q, wherein q is selected from the integers between 1 and 20, and when q is three or greater, (mannose)_q is selected from linear and branched structures.

- 15 29. A pharmaceutical composition comprising a pharmaceutically acceptable diluent and a remodeled peptide according to claim 1.

30. A cell-free, in vitro method of remodeling a peptide comprising poly(ethylene glycol), said peptide having the formula:



20

wherein

AA is a terminal or internal amino acid residue of said peptide;
X¹ is a glycosyl residue covalently linked to said AA, selected from
monosaccharyl and oligosaccharyl residues; and
u is an integer selected from 0 and 1,

5 said method comprising:

contacting said peptide with at least one glycosyltransferase and at least one
glycosyl donor under conditions suitable to transfer said at least one glycosyl donor to said
truncated glycan, thereby remodeling said peptide.

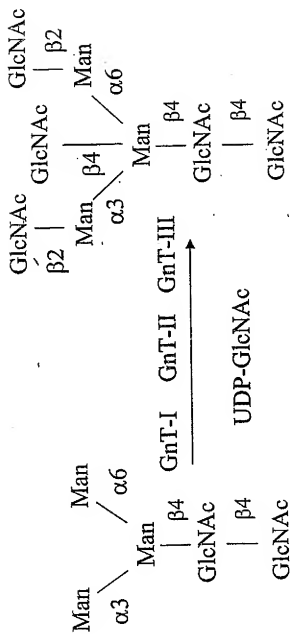
10 31. The method according to claim 30 wherein said at least one glycosyl
donor comprises a modifying group covalently linked thereto.

32. The method according to claim 30 wherein said modifying group is
poly(ethylene glycol).

15 33. The method according to claim 32 wherein said poly(ethylene glycol)
has a molecular weight distribution that is essentially homodisperse.

20 34. A pharmaceutical composition comprising a pharmaceutically
acceptable diluent and a remodeled peptide according to claim 30.

1/497

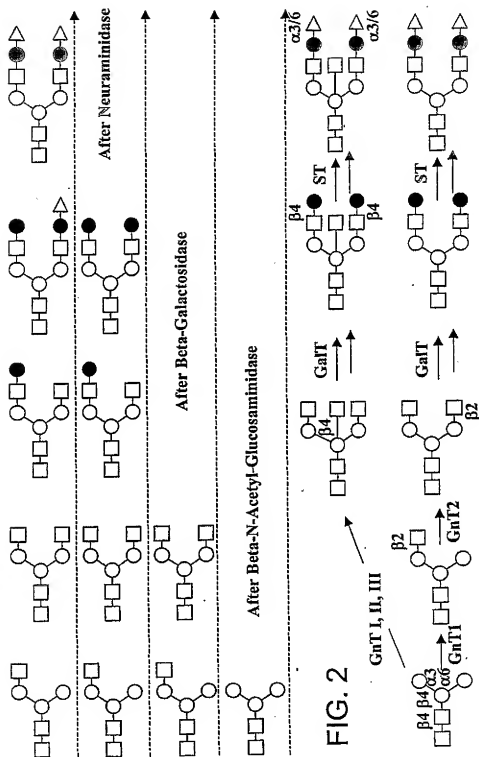


Trimannosyl core with
Bisecting GlcNAc

Trimannosyl core

FIG. 1

2/497



3/497

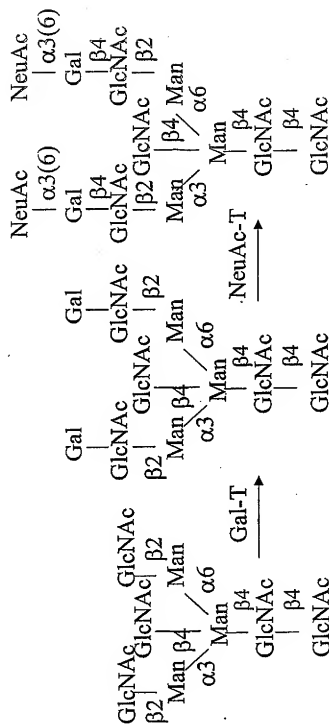


FIG. 3

4/497

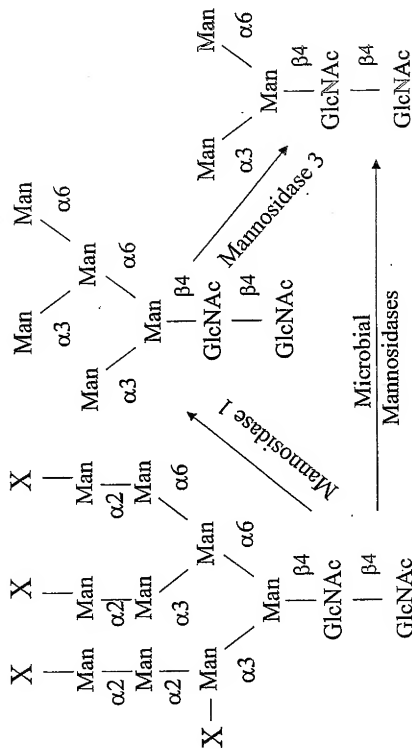


FIG. 4

5/497

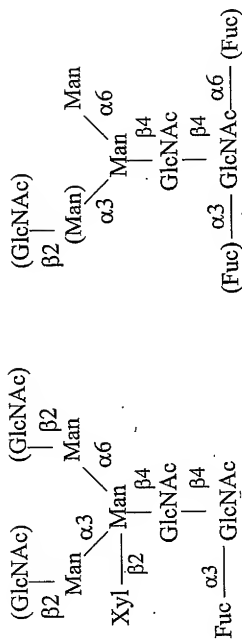


FIG. 6

FIG. 5

6/497

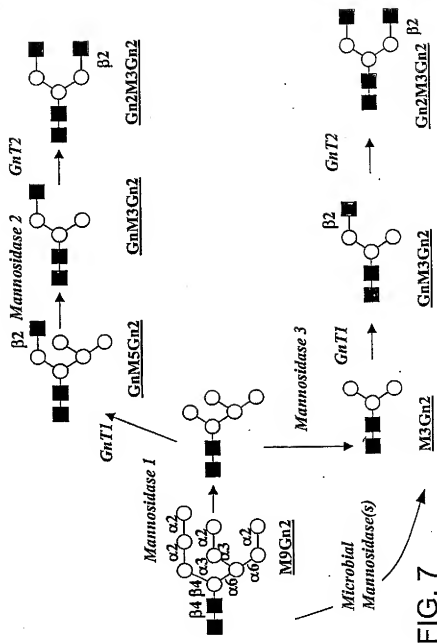


FIG. 7

7/497

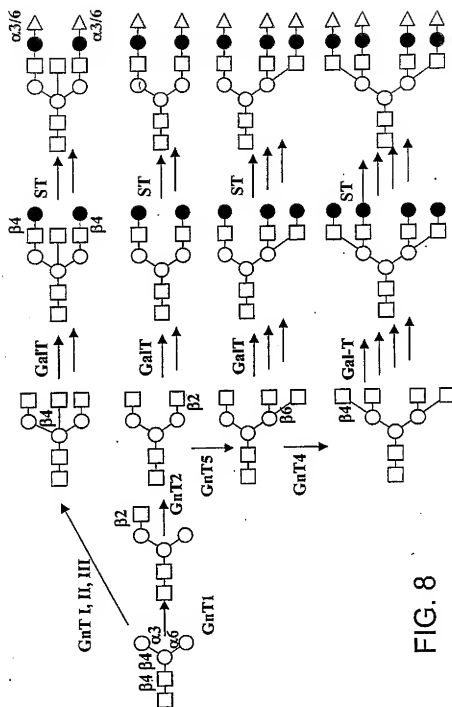


FIG. 8

8/497

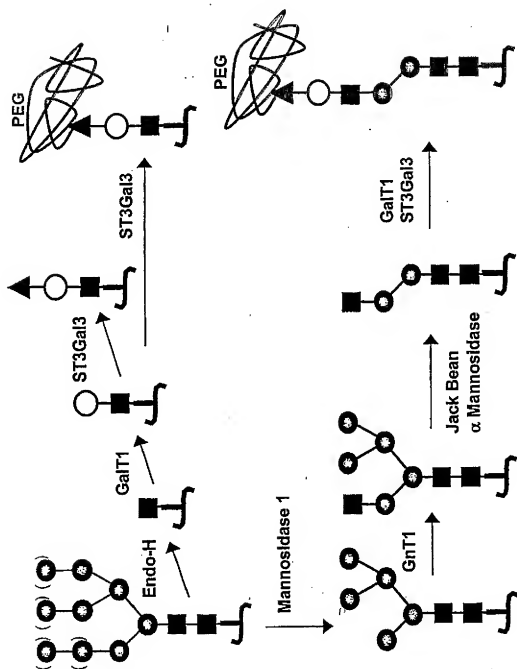


FIG. 9

9/497

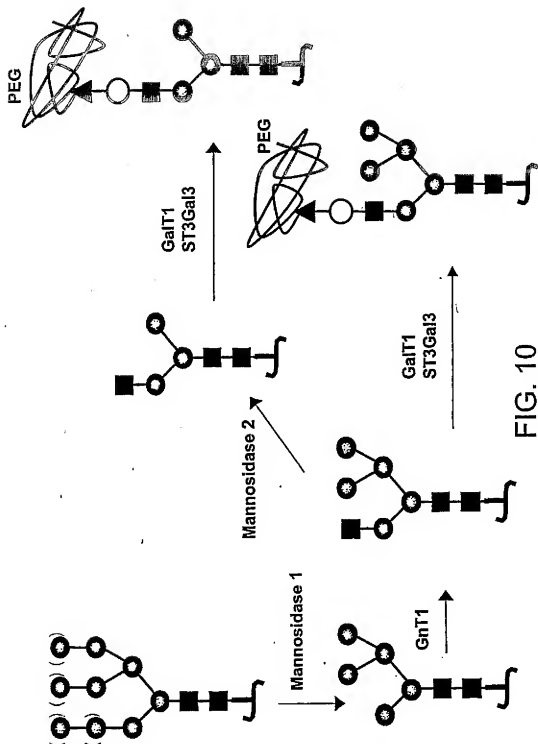


FIG. 10

10/497

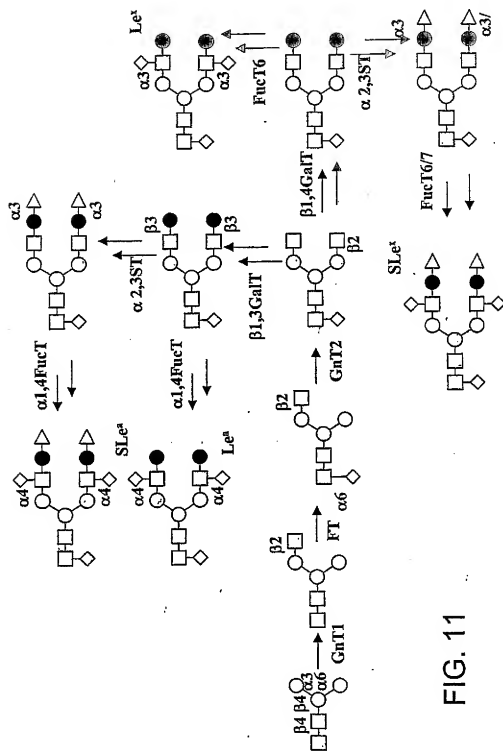


FIG. 11

11/497

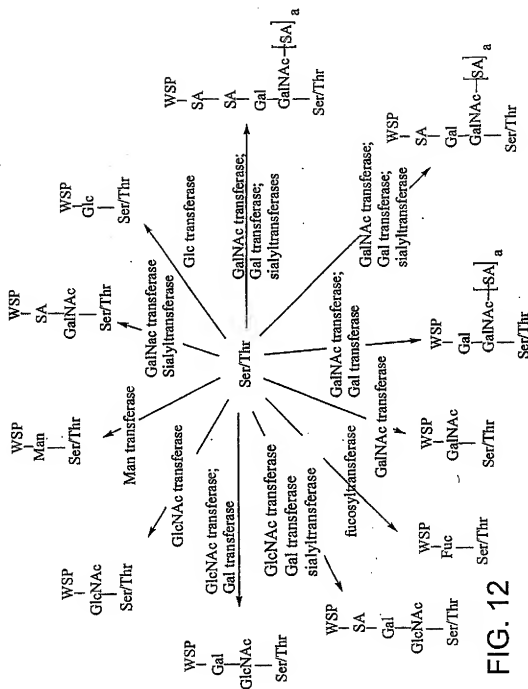


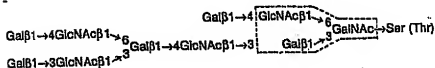
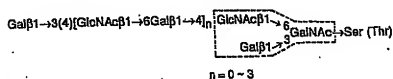
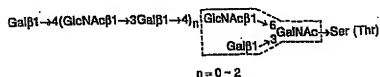
FIG. 12

12/497

Core 1



Core 2



Core 3



Core 4

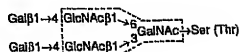


FIG. 13

15/497

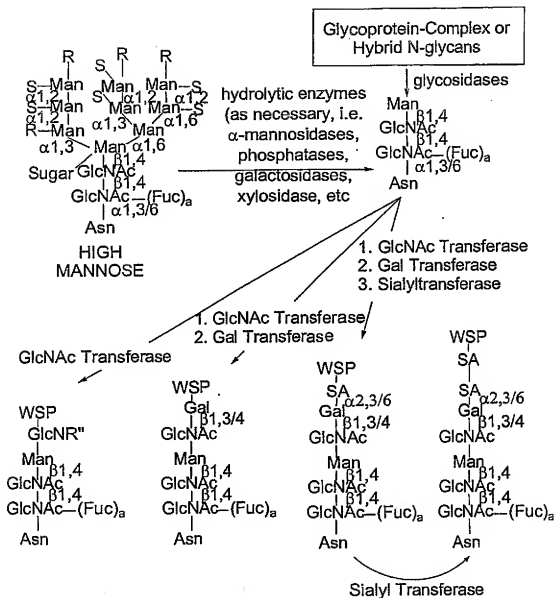


FIG. 15

16/497

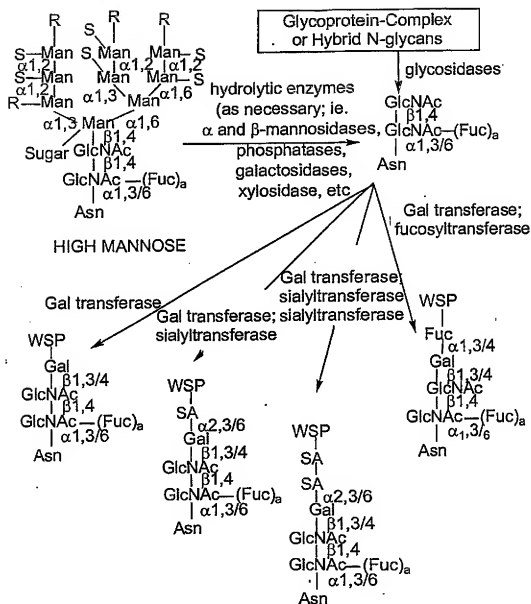


FIG. 16

17/497

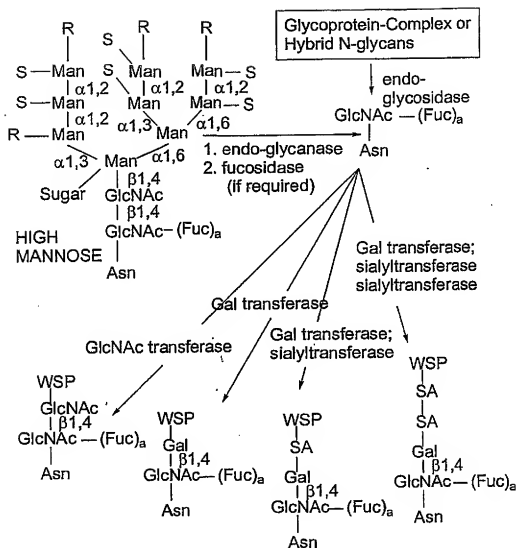
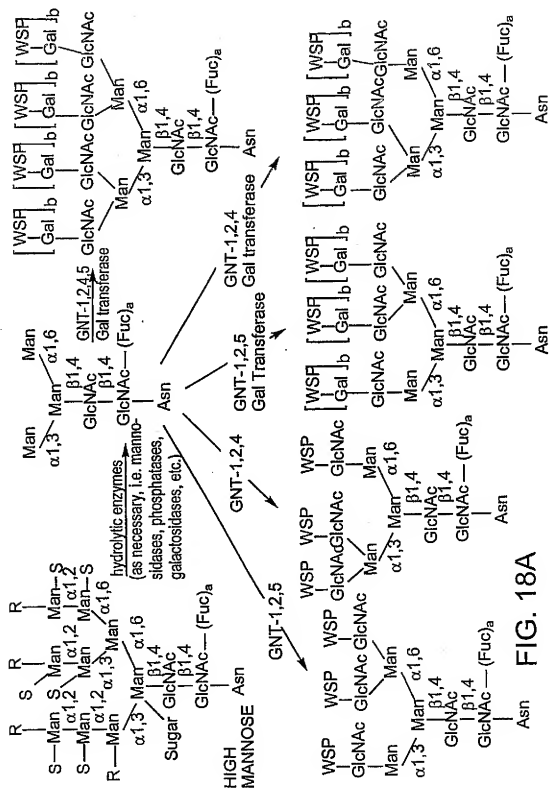


FIG. 17

18/497



19/497

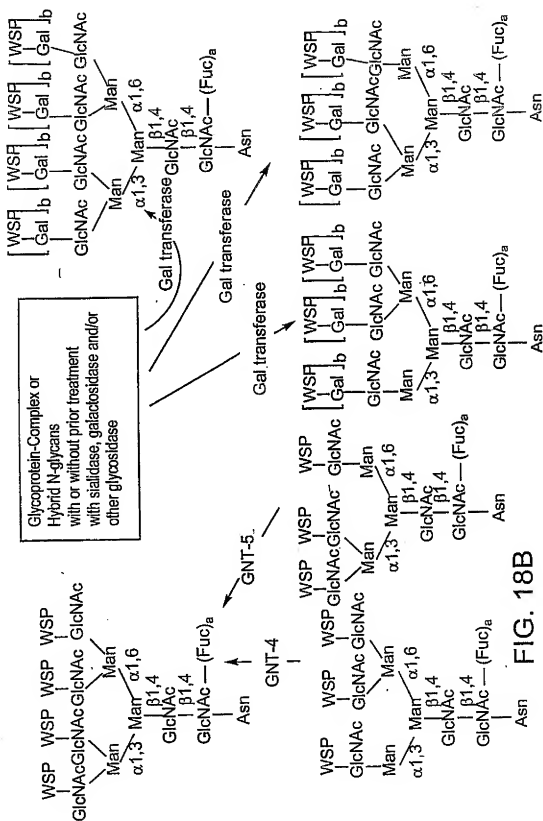


FIG. 18B

20/497

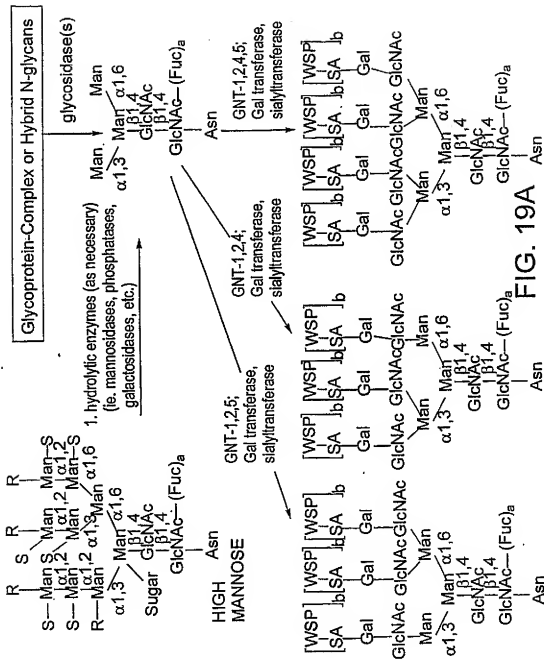
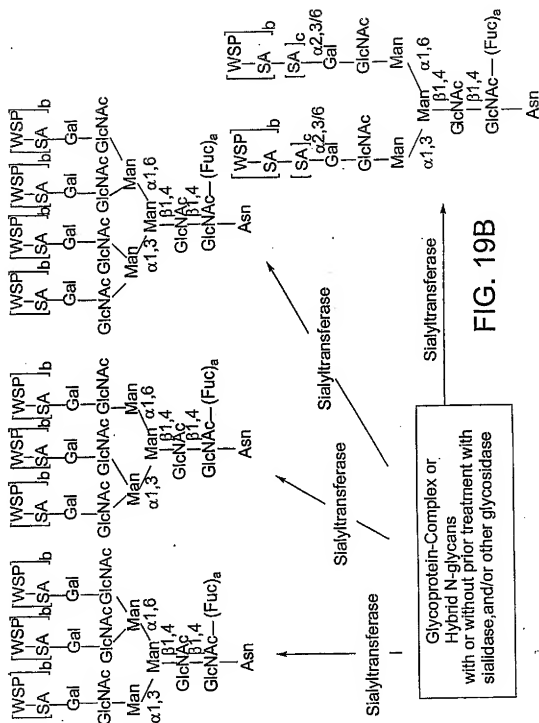


FIG. 19A

21/497



22/497

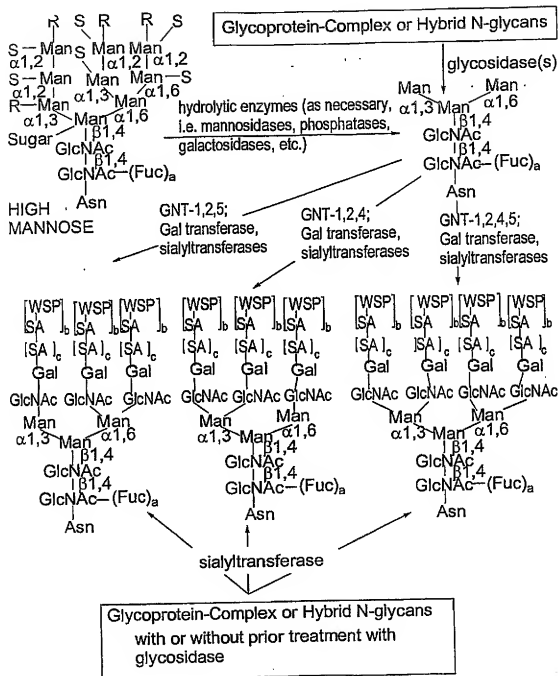
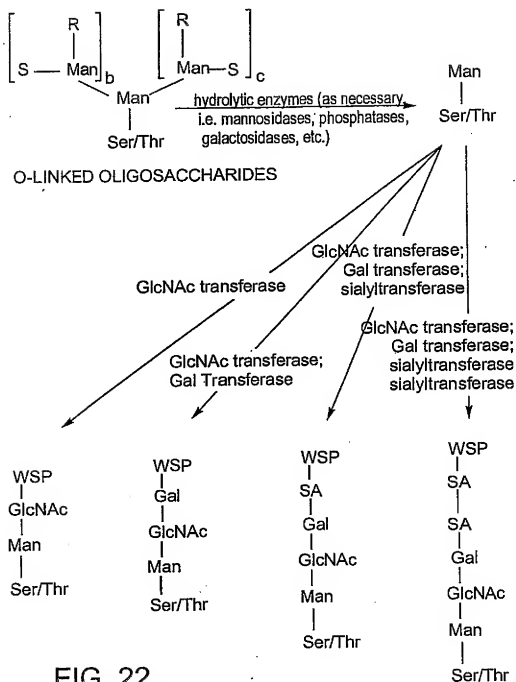


FIG. 20

24/497



25/497

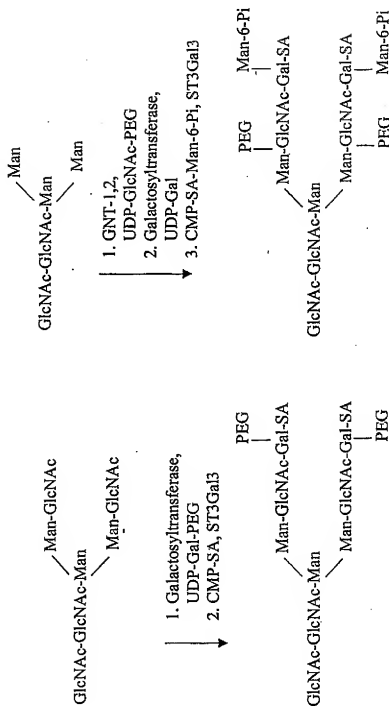


FIG. 23B

FIG. 23A

26/497

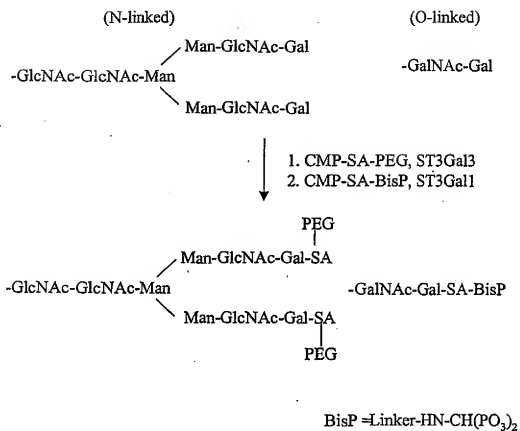


FIG. 23C

27/497

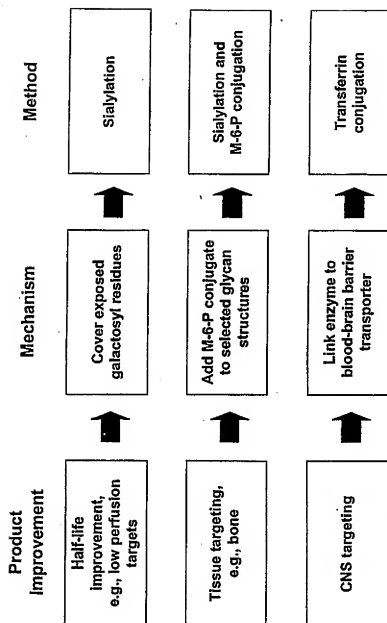


FIG. 24

28/497

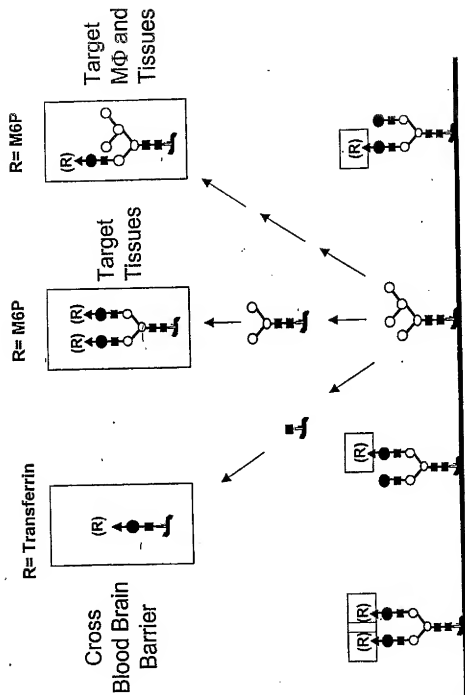


FIG. 25

29/497

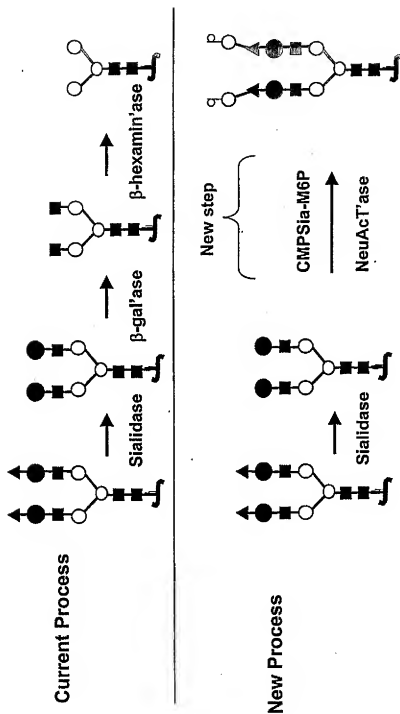


FIG. 26

30/497

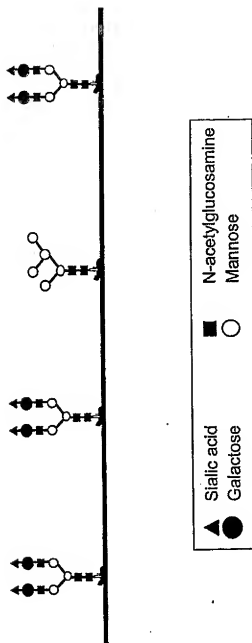


FIG. 27

31/497

12AP1/E5 -- Viventia Biotech
 1964 -- Aventis
 20K growth hormone -- AMUR
 28P6/E6 -- Viventia Biotech
 3-Hydroxyphthaloyl-beta-lactoglobulin --
 4-IBB ligand gene therapy --
 64-Cu MAb conjugate TETA-1A3 --
 Mallinckrodt Institute of Radiology
 64-Cu MAb conjugate TETA-cT84.66
 64-Cu Trastuzumab TETA conjugate --
 Genentech
 A 200 -- Amgen
 A10255 -- Eli Lilly
 A1PDX -- Hedral Therapeutics
 A6 -- Angstrom
 aaAT-III -- Genzyme
 Abciximab -- Centocor
 ABI.001 -- Atlantic BioPharmaceuticals
 ABT-828 -- Abbott
 Accutin
 Actinohivin
 activin -- Biotech Australia, Human
 Therapeutics, Curis
 AD 439 -- Tanox
 AD 519 -- Tanox
 Adalimumab -- Cambridge Antibody Tech.
 Adenocarcinoma vaccine -- Biomira -- NIS
 Adenosine deaminase -- Enzond
 Adenosine A2B receptor antagonists --
 Adenosine Therapeutics
 ADP-001 -- Axis Genetics
 AF 13948 -- Affymax
 Afelimomab -- Knoll
 AFP-SCAN -- Immunomedics
 AG 2195 -- Corixa
 agalsidase alfa -- Transkaryotic Therapies
 agalsidase beta -- Genzyme
 AGENT-- Antisoma
 AI 300 -- AutoImmune
 AI-101 -- Teva
 AI-102 -- Teva
 AI-201 -- AutoImmune
 AI-301 -- AutoImmune
 AIDS vaccine -- ANRS, CIBG, Hesel
 Biomed, Hollis-Eden, Rome, United
 Biomedical, American Home Products,
 Maxygen
 airway receptor ligand -- IC Innovations
 AJvW 2 -- Ajinomoto
 AK 30 NGF -- Alkermes
 Albuferon -- Human Genome Sciences
 albumin -- Biogen, DSM Anti-Infectives,
 Genzyme Transgenics, PPL Therapeutics,
 TranXenoGen, Welfide Corp.
 aldesleukin -- Chiron
 alefacept -- Biogen
 Alemtuzumab
 Allergy therapy -- ALK-Abello/Maxygen,
 ALK-Abello/RP Scherer
 allergy vaccines -- Allergy Therapeutics
 Alnidofibatide -- Aventis Pasteur
 Alnorine -- SRC VB VECTOR
 ALP 242 -- Gruenenthal
 Alpha antitrypsin -- Arriva/Hyland
 Immuno/ProMetic/Protease Sciences
 Alpha-1 antitrypsin -- Cutter, Bayer, PPL
 Therapeutics, Profile, ZymoGenetics,
 Arriva
 Alpha-1 protease inhibitor -- Genzyme
 Transgenics, Welfide Corp.
 Alpha-galactose fusion protein --
 Immunomedics
 Alpha-galactosidase A -- Research
 Corporation Technologies, Genzyme
 Alpha-glucosidase -- Genzyme, Novazyme
 Alpha-lactalbumin
 Alpha-L-iduronidase -- Transkaryotic
 Therapies, BioMarin
 alteplase -- Genentech
 alvircept sudotox -- NIH
 ALX1-11 -- sNPS Pharmaceuticals
 Alzheimer's disease gene therapy

FIG. 28A

32/497

AM-133 -- AMRAD
 Amb a 1 immunostim conj. -- Dynavax
 AMD 3100 -- AnorMED -- NIS
 AMD 3465 -- AnorMED -- NIS
 AMD 3465 -- AnorMED -- NIS
 AMD Fab -- Genentech
 Amediplase -- Menarini, Novartis
 AM-F9
 Amoebiasis vaccine
 Amphiregulin -- Octagene
 anakinra -- Amgen
 analgesic -- Nobex
 anacem -- Amgen
 AnergiX.RA -- Corixa, Organon
 Angiocidin -- InKine
 angiogenesis inhibitors -- ILEX
 AngioMab -- Antisoma
 Angiopoietins -- Regeneron/Procter & Gamble
 angiotatin -- EntreMed
 Angiotatin/endostatin gene therapy -- Genetix Pharmaceuticals
 angiotensin-II, topical -- Maret
 Anthrax -- EliSys Therapeutics/US Army Medical Research Institute
 Anthrax vaccine
 Anti platelet-derived growth factor D human monoclonal antibodies -- CuraGen
 Anti-17-1A MAb 3622W94 -- GlaxoSmithKline
 Anti-2C4 MAb -- Genentech
 anti-4-1BB monoclonal antibodies -- Bristol-Myers Squibb
 Anti-Adhesion Platform Tech. -- Cytovax
 Anti-adipocyte MAb -- Cambridge Antibody Tech./ObesSys
 antiallergics -- Maxygen
 antiallergy vaccine -- Acambis
 Anti-alpha-4-integrin MAb
 Anti-alpha-v β 3 integrin MAb -- Applied Molecular Evolution
 Anti-angiogenesis monoclonal antibodies -- KS Biomedix/Schering AG
 Anti-B4 MAb-DC1 conjugate -- ImmunoGen
 Anti-B7 antibody PRIMATIZED -- IDEC
 Anti-B7-1 MAb 16-10A1
 Anti-B7-1 MAb 1G10
 Anti-B7-2 MAb GL-1
 Anti-B7-2-gelonin immunotoxin -- Antibacterials/antifungals -- Diversa/IntraBiotics
 Anti-beta-amyloid monoclonal antibodies -- Cambridge Antibody Tech., Wyeth-Ayerst
 Anti-BLyS antibodies -- Cambridge Antibody Tech./Human Genome Sciences
 Antibody-drug conjugates -- Seattle Genetics/Eos
 Anti-C5 MAb BB5-1 -- Alexion
 Anti-C5 MAb N19-8 -- Alexion
 Anti-C8 MAb
 anticancer cytokines -- BioPulse
 anticancer matrix -- Telios Integra
 Anticancer monoclonal antibodies -- ARIUS, Immunex
 anticancer peptides -- Maxygen, Micrologix
 Anticancer prodrug Tech. -- Alexion
 Antibody Technologies
 anticancer Troy-Bodies -- Affite -- Affitech
 anticancer vaccine -- NIH
 anticancers -- Epimmune
 Anti-CCR5/CXCR4 sheep MAb -- KS Biomedix Holdings
 Anti-CD11a MAb KBA --
 Anti-CD11a MAb M17
 Anti-CD11a MAb TA-3 --
 Anti-CD11a MAb WT.1 --
 Anti-CD11b MAb -- Pharmacia
 Anti-CD11b MAb LM2
 Anti-CD154 MAb -- Biogen
 Anti-CD16-anti-CD30 MAb -- Biotest
 Anti-CD18 MAb -- Pharmacia
 Anti-CD19 MAb B43 --

FIG. 28B

33/497

Anti-CD19 MAb -liposomal sodium butyrate conjugate -	Anti-CD4 MAb 4162W94 - GlaxoSmithKline
Anti-CD147	Anti-CD4 MAb B-F5 - Diaclone
Anti-CD19 MAb-saporin conjugate -	Anti-CD4 MAb GK1-5
Anti-CD19-dsFv-PE38-immunotoxin -	Anti-CD4 MAb KT6
Anti-CD2 MAb 12-15 -	Anti-CD4 MAb OX38
Anti-CD2 MAb B-E2 - Diaclone	Anti-CD4 MAb PAP conjugate - Bristol-Myers Squibb
Anti-CD2 MAb OX34 -	Anti-CD4 MAb RIB 5-2
Anti-CD2 MAb OX54 -	Anti-CD4 MAb W3/25
Anti-CD2 MAb OX55 -	Anti-CD4 MAb YTA 3.1.2
Anti-CD2 MAb RM2-1	Anti-CD4 MAb YTS 177-9
Anti-CD2 MAb RM2-2	Anti-CD40 ligand MAb 5c8 - Biogen
Anti-CD2 MAb RM2-4	Anti-CD40 MAb
Anti-CD20 MAb BCA B20	Anti-CD40 MAb 5D12 - Tanox
Anti-CD20-anti-Fc alpha RI bispecific MAb - Medarex, Tenovus	Anti-CD44 MAb A3D8
Anti-CD22 MAb-saporin-6 complex -	Anti-CD44 MAb GKWA3
Anti-CD3 immunotoxin -	Anti-CD44 MAb IM7
Anti-CD3 MAb 145-2C11 - Pharming	Anti-CD44 MAb KM81
Anti-CD3 MAb CD4IgG conjugate - Genentech	Anti-CD44 variant monoclonal antibodies - Corixa/Hebrew University
Anti-CD3 MAb humanised - Protein Design, RW Johnson	Anti-CD45 MAb BC8-I-131
Anti-CD3 MAb WT32	Anti-CD45RB MAb
Anti-CD3 MAb-ricin-chain-A conjugate -	Anti-CD48 MAb HuLy-m3
Anti-CD3 MAb-xanthine-oxidase conjugate -	Anti-CD48 MAb WM-63
	Anti-CD5 MAb - Becton Dickinson
Anti-CD30 MAb BerH2 - Medac	Anti-CD5 MAb OX19
Anti-CD30 MAb-saporin conjugate	Anti-CD6 MAb
Anti-CD30-scFv-ETA'-immunotoxin	Anti-CD7 MAb-PAP conjugate
Anti-CD38 MAb AT13/5	Anti-CD7 MAb-ricin-chain-A conjugate
Anti-CD38 MAb-saporin conjugate	Anti-CD8 MAb - Amerimmune, Cytodyn, Becton Dickinson
Anti-CD3-anti-CD19 bispecific MAb	Anti-CD8 MAb 2-43
Anti-CD3-anti-EGFR MAb	Anti-CD8 MAb OX8
Anti-CD3-anti-interleukin-2-receptor MAb	Anti-CD80 MAb P16C10 - IDEC
Anti-CD3-anti-MOV18 MAb - Centocor	Anti-CD80 MAb P7C10 - ID Vaccine
Anti-CD3-anti-SCLC bispecific MAb	Anti-CD8-idarubicin conjugate
Anti-CD4 idiotype vaccine	Anti-CEA MAb CE-25
Anti-CD4 MAb - Centocor, IDEC Pharmaceuticals, Xenova Group	Anti-CEA MAb MN 14 - Immunomedics
Anti-CD4 MAb 16H5	Anti-CEA MAb MN14-PE40 conjugate - Immunomedics

FIG. 28C

34/497

Anti-CEA MAb T84.66-interleukin-2 conjugate
 Anti-CEA sheep MAb -- KS Biomedix Holdings
 Anti-cell surface monoclonal antibodies -- Cambridge Antibody Tech. /Pharmacia
 Anti-c-erbB2-anti-CD3 bifunctional MAb -- Otsuka
 Anti-CMV MAb -- Scotgen
 Anti-complement
 Anti-CTLA-4 MAb
 Anti-EGFR catalytic antibody -- Heses Biomed
 anti-EGFR immunotoxin -- IVAX
 Anti-EGFR MAb -- Abgenix
 Anti-EGFR MAb 528
 Anti-EGFR MAb KSB 107 -- KS Biomedix
 Anti-EGFR MAb-DM1 conjugate -- ImmunoGen
 Anti-EGFR MAb-LA1 --
 Anti-EGFR sheep MAb -- KS Biomedix
 Anti-FAP MAb F19-I-131
 Anti-Fas IgM MAb CH11
 Anti-Fas MAb Jo2
 Anti-Fas MAb RK-8
 Anti-FIT-1 monoclonal antibodies -- ImClone
 Anti-fungal peptides -- State University of New York
 antifungal tripeptides -- BTG
 anti-ganglioside GD2 antibody-interleukin-2 fusion protein -- Lexigen
 Anti-GM2 MAb -- Kyowa
 Anti-GM-CSF receptor monoclonal antibodies -- AMRAD
 Anti-gp130 MAb -- Tosoh
 Anti-HCA monoclonal antibodies -- AltaRex/Epigen
 Anti-hCG antibodies -- Abgenix/AVI BioPharma
 Anti-heparanase human monoclonal antibodies -- Oxford Glycosciences/Medarex
 Anti-hepatitis C virus human monoclonal antibodies -- XTL Biopharmaceuticals
 Anti-HER-2 antibody gene therapy
 Anti-herpes antibody -- Epicyte
 Anti-HIV antibody -- Epicyte
 Anti-HIV catalytic antibody -- Heses Biomed
 anti-HIV fusion protein -- Idun
 anti-HIV proteins -- Cangene
 Anti-HM1-24 MAb -- Chugai
 Anti-hR3 MAb
 Anti-Human-Carcinoma-Antigen MAb -- Epicyte
 Anti-ICAM-1 MAb -- Boehringer Ingelheim
 Anti-ICAM-1 MAb 1A-29 -- Pharmacia
 Anti-ICAM-1 MAb HA58
 Anti-ICAM-1 MAb YN1/1.7.4
 Anti-ICAM-3 MAb ICM3 -- ICOS
 Anti-idiotype breast cancer vaccine 11D10
 Anti-idiotype breast cancer vaccine ACA14C5 --
 Anti-idiotype cancer vaccine -- ImClone Systems/Merck KGaA ImClone, Viventia Biotech
 Anti-idiotype cancer vaccine 1A7 -- Titan
 Anti-idiotype cancer vaccine 3H1 -- Titan
 Anti-idiotype cancer vaccine TriAb -- Titan
 Anti-idiotype Chlamydia trachomatis vaccine
 Anti-idiotype colorectal cancer vaccine -- Novartis
 Anti-idiotype colorectal cancer vaccine -- Onyvax
 Anti-idiotype melanoma vaccine -- IDEC Pharmaceuticals
 Anti-idiotype ovarian cancer vaccine ACA 125
 Anti-idiotype ovarian cancer vaccine AR54 - AltaRex

FIG. 28D

35/497

Anti-idiotypic ovarian cancer vaccine CA-125 -- AltaRex, Biomira	Anti-L-selectin monoclonal antibodies -- Protein Design Labs, Abgenix, Stanford University
Anti-IgE catalytic antibody -- Hesel Biomed	Anti-MBL monoclonal antibodies -- Alexion/Brigham and Women's Hospital
Anti-IgE MAb E26 -- Genentech	Anti-MHC monoclonal antibodies
Anti-IGF-1 MAb	Anti-MIF antibody humanised -- IDEC, Cytokine PharmaSciences
anti-inflammatory -- GeneMax	Anti-MRSA/VRSA sheep MAb -- KS Biomedix Holdings
anti-inflammatory peptide -- BTG	Anti-mu MAb -- Novartis
anti-integrin peptides -- Burnha	Anti-MUC-1 MAb
Anti-interferon-alpha-receptor MAb 64G12 -- Pharma Pacific Management	Anti-MUC 18
Anti-interferon-gamma MAb -- Protein Design Labs	Anti-Nogo-A MAb 1N1
Anti-interferon-gamma polyclonal antibody -- Advanced Biotherapy	Anti-nuclear autoantibodies -- Procyon
Anti-interleukin-10 MAb --	Anti-ovarian cancer monoclonal antibodies -- Dompe
Anti-interleukin-12 MAb --	Anti-p185 monoclonal antibodies
Anti-interleukin-1-beta polyclonal antibody -- R&D Systems	Anti-p43 MAb
Anti-interleukin-2 receptor MAb 2A3	Antiparasitic vaccines
Anti-interleukin-2 receptor MAb 33B3-1 -- Immunotech	Anti-PDGF/bFGF sheep MAb -- KS Biomedix
Anti-interleukin-2 receptor MAb ART-18	Anti-properdin monoclonal antibodies -- Abgenix/Gliatech
Anti-interleukin-2 receptor MAb LO-Tact-1	Anti-PSMA (prostate specific membrane antigen)
Anti-interleukin-2 receptor MAb Mikbeta1	Anti-PSMA MAb J591 -- BZL Biologics
Anti-interleukin-2 receptor MAb NDS61	Anti-Rev MAb gene therapy --
Anti-interleukin-4 MAb 11B11	Anti-RSV antibodies -- Epicycle, Intracell
Anti-interleukin-5 MAb -- Wallace Laboratories	Anti-RSV monoclonal antibodies -- Medarex/MedImmune, Applied Molecular Evolution/MedImmune
Anti-interleukin-6 MAb -- Centocor, Diaclone, Pharmadigm	Anti-RSV MAb, inhalation -- Alkermes/MedImmune
Anti-interleukin-8 MAb -- Abgenix	Anti-RT gene therapy
Anti-interleukin-8 MAb -- Xenotech	Antisense K-ras RNA gene therapy
Anti-JL1 MAb	Anti-SF-25 MAb
Anti-Klebsiella sheep MAb -- KS Biomedix Holdings	Anti-sperm antibody -- Epicycle
Anti-Laminin receptor MAb-liposomal doxorubicin conjugate	Anti-Tac(Fv)-PE38 conjugate
Anti-LCG MAb -- Cytoclonal	Anti-TAPA/CD81 MAb AMP1
Anti-lipopolysaccharide MAb -- VitaResc	Anti-tat gene therapy

FIG. 28E

36/497

Anti-TCR-alphabeta MAb H57-597	AOP-RANTES – Senetek
Anti-TCR-alphabeta MAb R73	Apan-CH – Praecis Pharmaceuticals
Anti-tenascin MAb BC-4-I-131	APC-8024 – Demegen
Anti-TGF-beta human monoclonal antibodies – Cambridge Antibody Tech., Genzyme	ApoA-1 – Milano, Pharmacia
Anti-TGF-beta MAb 2G7 – Genentech	Apogen – Alexion
Antithrombin III – Genzyme Transgenics, Aventis, Bayer, Behringwerke, CSL, Myriad	apolipoprotein A1 – Avanir
Anti-Thy1 MAb	Apolipoprotein E – Bio-Tech. General
Anti-Thy1.1 MAb	Applaggin – Biogen
Anti-tissue factor/factor VIIA sheep MAb – KS Biomedix	aprotinin – ProdiGene
Anti-TNF monoclonal antibodies – Centocor, Chiron, Peptech, Pharmacia, Serono	APT-070C – AdProTech
Anti-TNF sheep MAb – KS Biomedix Holdings	AR 177 – Aronex Pharmaceuticals
Anti-TNFalpha MAb – Genzyme	AR 209 – Aronex Pharmaceuticals, Antigenics
Anti-TNFalpha MAb B-C7 – Diaclone	AR545C
Anti-tooth decay MAb – Planet BioTech.	ARGENT gene delivery systems – ARIAD
Anti-TRAIL receptor-1 MAb – Takeda	Arresten
Antitumour RNases – NIH	ART-123 – Asahi Kasei
Anti-VCAM MAb 2A2 – Alexion	arylsulfatase B – BioMarin
Anti-VCAM MAb 3F4 – Alexion	Arylsulfatase B, Recombinant human – BioMarin
Anti-VCAM-1 MAb	AS 1051 – Ajinomoto
Anti-VEC MAb – ImClone	ASI-BCL – Intracell
Anti-VEGF MAb – Genentech	Asparaginase – Merck
Anti-VEGF MAb 2C3	ATL-101 – Alizyme
Anti-VEGF sheep MAb – KS Biomedix Holdings	Atrial natriuretic peptide – Pharis
Anti-VLA-4 MAb HP1/2 – Biogen	Aurintricarboxylic acid-high molecular weight
Anti-VLA-4 MAb PS/2	Autoimmune disorders – GPC
Anti-VLA-4 MAb R1-2	Biotech/MorphoSys
Anti-VLA-4 MAb TA-2	Autoimmune disorders and transplant rejection – Bristol-Myers Squibb/Genzyme
Anti-VAP-1 human MAb	Tra
Anti-VRE sheep MAb – KS Biomedix Holdings	Autoimmune disorders/cancer – Abgenix/Chiron, CuraGen
ANUP – TranXenoGen	Autotaxin
ANUP-1 – Pharis	Avicidin – NeoRx
	axogenesis factor-1 – Boston Life Sciences
	Axokine – Regeneron
	B cell lymphoma vaccine – Biomira
	B7-1 gene therapy –
	BABS proteins – Chiron

FIG. 28F

37/497

BAM-002 -- Novelos Therapeutics
 Basiliximab (anti CD25 MAb) -- Novartis
 Bay-16-9996 -- Bayer
 Bay-39-9437 -- Bayer
 Bay-50-4798 -- Bayer
 BB-10153 -- British Biotech
 BBT-001 -- Bolder BioTech.
 BBT-002 -- Bolder BioTech.
 BBT-003 -- Bolder BioTech.
 BBT-004 -- Bolder BioTech.
 BBT-005 -- Bolder BioTech.
 BBT-006 -- Bolder BioTech.
 BBT-007 -- Bolder BioTech.
 BCH-2763 -- Shire
 BCSF -- Millenium Biologix
 BDNF -- Regeneron -- Amgen
 Becaplermin -- Johnson & Johnson, Chiron
 Bectumomab -- Immunomedics
 Beriplast -- Aventis
 Beta-adrenergic receptor gene therapy --
 University of Arkansas
 bFGF -- Scios
 BI 51013 -- Behringwerke AG
 BIBH 1 -- Boehringer Ingelheim
 BIM-23190 -- Beaufour-Ipsen
 birch pollen immunotherapy -- Pharmacia
 bispecific fusion proteins -- NIH
 Bispecific MAb 2B1 -- Chiron
 Bitistatin
 BIWA 4 -- Boehringer Ingelheim
 blood substitute -- Northfield, Baxter Intl.
 BLP-25 -- Biomira
 BLS-0597 -- Boston Life Sciences
 BLYS -- Human Genome Sciences
 BLYS radiolabelled -- Human Genome
 Sciences
 BM 06021 -- Boehringer Mannheim
 BM-202 -- BioMarin
 BM-301 -- BioMarin
 BM-301 -- BioMarin
 BM-302 -- BioMarin
 BMP 2 -- Genetics Institute/Medtronic-
 Sofamor Danek, Genetics Institute/
 Collagenesis, Genetics
 Institute/Yamanouch
 BMP 2 gene therapy
 BMP 52 -- Aventis Pasteur, Biopharm
 BMP-2 -- Genetics Institute
 BMS 182248 -- Bristol-Myers Squibb
 BMS 202448 -- Bristol-Myers Squibb
 bone growth factors -- IsoTis
 BPC-15 -- Pfizer
 brain natriuretic peptide --
 Breast cancer -- Oxford
 GlycoSciences/Medarex
 Breast cancer vaccine -- Therion Biologics,
 Oregon
 BSSL -- PPL Therapeutics
 BST-2001 -- BioStratum
 BST-3002 -- BioStratum
 BTI 322 --
 butyrylcholinesterase -- Shire
 C 6822 -- COR Therapeutics
 C1 esterase inhibitor -- Pharming
 C3d adjuvant -- AdProTech
 CAB-2.1 -- Millennium
 calcitonin -- Inhale Therapeutics Systems,
 Aventis, Genetronics, TranXenoGen,
 Unigene, Rhone Poulenc Rohrer
 calcitonin -- oral -- Nobex, Emisphere,
 Pharmaceutical Discovery
 Calcitonin gene-related peptide -- Asahi
 Kasei -- Unigene
 calcitonin, human -- Suntory
 calcitonin, nasal -- Novartis, Unigene
 calcitonin, Panoderm -- Elan
 calcitonin, Peptitrol -- Shire
 calcitonin, salmon -- Therapicon
 calin -- Biopharm
 Calphobindin I
 calphobindin I -- Kowa
 calreticulin -- NYU

FIG. 28G

38/497

Campath-1G
 Campath-1M
 cancer therapy -- Cangene
 cancer vaccine -- Aixlie, Aventis Pasteur,
 Center of Molecular Immunology, YMI
 BioSciences, Cytos, Genzyme,
 Transgenics, GlobeImmune, Igeneon;
 ImClone, Virogenetics, InterCell, Iomai,
 Jenner Biotherapies, Memorial Sloan-
 Kettering Cancer Center, Sydney Kimmel
 Cancer Center, Novavax, Protein
 Sciences, Argonex, SIGA
 Cancer vaccine ALVAC-CEA B7.1 --
 Aventis Pasteur/Therion Biologics
 Cancer vaccine CEA-TRICOM -- Aventis
 Pasteur/Therion Biologics
 Cancer vaccine gene therapy -- Cantab
 Pharmaceuticals
 Cancer vaccine HER-2/neu -- Corixa
 Cancer vaccine THERATOPE -- Biomira
 cancer vaccine, PolyMASC -- Valentis
 Candida vaccine -- Corixa, Inhibitex
 Canstatin -- ILEX
 CAP-18 -- Panorama
 Cardiovascular gene therapy -- Collateral
 Therapeutics
 carperitide -- Suntory
 Casocidin-1 -- Pharis
 CAT 152 -- Cambridge Antibody Tech.
 CAT 192 -- Cambridge Antibody Tech.
 CAT 213 -- Cambridge Antibody Tech.
 Catalase -- Enzon
 Cat-PAD -- Circassia
 CB 0006 -- Celltech
 CCK(27-32) -- Akzo Nobel
 CCR2-641 -- NIH
 CD, Procept -- Paligent
 CD154 gene therapy
 CD39 -- Immunex
 CD39-L2 -- Hyseq
 CD39-L4 -- Hyseq
 CD4 fusion toxin -- Senetek
 CD4 IgG -- Genentech
 CD4 receptor antagonists --
 PharmacoPeia/Progenics
 CD4 soluble -- Progenics
 CD4, soluble -- Genzyme Transgenics
 CD40 ligand -- Immunex
 CD4-ricin chain A -- Genentech
 CD59 gene therapy -- Alexion
 CD8 TIL cell therapy -- Aventis Pasteur
 CD8, soluble -- Avidex
 CD95 ligand -- Roche
 CDP 571 -- Celltech
 CDP 850 -- Celltech
 CDP-860 (PEG-PDGF MAb) -- Celltech
 CDP 870 -- Celltech
 CDS-1 -- Ernest Orlando
 Cedelizumab -- Ortho-McNeil
 Cetermin -- Insmad
 CETP vaccine -- Avant
 Cetorelix
 Cetuximab
 CGH 400 -- Novartis
 CGP 42934 -- Novartis
 CGP 51901 -- Tanox
 CGRP -- Unigene
 CGS 27913 -- Novartis
 CGS 32359 -- Novartis
 Chagas disease vaccine -- Corixa
 chemokines -- Immune Response
 CHH 380 -- Novartis
 chitinase -- Genzyme, ICOS
 Chlamydia pneumoniae vaccine -- Antex
 Biologics
 Chlamydia trachomatis vaccine -- Antex
 Biologics
 Chlamydia vaccine -- GlaxoSmithKline
 Cholera vaccine CVD 103-HgR -- Swiss
 Serum and Vaccine Institute Berne
 Cholera vaccine CVD 112 -- Swiss Serum
 and Vaccine Institute Berne

FIG. 28H

39/497

Cholera vaccine inactivated oral – SBL	CRL 1605 – CytRx
Vaccin	CS-560 – Sankyo
Chrysalin – Chrysalis BioTech.	CSF – ZymoGenetics
CI-782 – Hitachi Kase	CSF-G – Hangzhou, Dong-A, Hanmi
Ciliary neurotrophic factor – Fidia, Roche	CSF-GM – Cangene, Hunan, LG Chem
CIM project – Active Biotech	CSF-M – Zarix
CL 329753 – Wyeth-Ayerst	CT 1579 – Merck Frosst
CL22, Cobra – ML Laboratories	CT 1786 – Merck Frosst
Clenoliximab – IDEC	CT-112 ^A – BTG
Clostridium difficile antibodies – Epicyte	CTB-134L – Xenova
clotting factors – Octagene	CTC-111 – Kaketsuken
CMB 401 – Celltech	CTGF – FibroGen
CNTF – Sigma-Tau	CTLA4-Ig – Bristol-Myers Squibb
Cocaine abuse vaccine – Cantab,	CTLA4-Ig gene therapy –
ImmuLogic, Scripps	CTP-37 – AVI BioPharma
coccidiomycosis vaccine – Arizo	C-type natriuretic peptide – Suntory
collagen – Type I – Pharming	CVS 995 – Corvas Intl.
Collagen formation inhibitors – FibroGen	CX 397 – Nikko Kyodo
Collagen/hydroxyapatite/bone growth factor	CY 1747 – Epimmune
– Aventis Pasteur, Biopharm, Orquest	CY 1748 – Epimmune
collagenase – BioSpecifics	Cyanovirin-N
Colorectal cancer vaccine – Wistar Institute	Cystic fibrosis therapy – CBR/IVAX
Component B, Recombinant – Sero	CYT 351
Connective tissue growth factor inhibitors –	cytokine Traps – Regeneron
FibroGen/Taisho	cytokines – Enzon, Cytoconal
Contortrostatin	Cytomegalovirus glycoprotein vaccine –
contraceptive vaccine – Zonagen	Chiron, Aquila Biopharmaceuticals,
Contraceptive vaccine hCG	Aventis Pasteur, Virogenetics
Contraceptive vaccine male reversible –	Cytomegalovirus vaccine live – Aventis
IMMUCON	Pasteur
Contraceptive vaccine zona pellucida –	Cytosine deaminase gene therapy –
Zonagen	GlaxoSmithKline
Copper-64 labelled MAb TETA-1A3 – NCI	DA-3003 – Dong-A
Coralyn	DAB389interleukin-6 – Senetek
Corsein M	DAB389interleukin-7
C-peptide analogues – Schwarz	Daclizumab (anti-IL2R MAb) – Protein
CPI-1500 – Consensus	Design Labs
CRF – Neurobiological Tech.	DAMP ^A – Incyte Genomics
cRGDFV pentapeptide –	Daniplestim – Pharmacia
CRL 1095 – CytRx	darbepoetin alfa – Amgen
CRL 1336 – CytRx	DBI-3019 – Diabetogen

FIG. 281

40/497

DCC -- Genzyme
 DDF -- Hyseq
 decarin -- Integra, Telios
 defensins -- Large Scale Biology
 DEGR-VIIa
 Deimmunised antibody 3B6/22 AGEN
 Deimmunised anti-cancer antibodies --
 Biovation/Viragen
 Dendroamide A
 Dengue vaccine -- Bavarian Nordic, Merck
 denileukin difitox -- Ligand
 DES-1101 -- Desmos
 desirudin -- Novartis
 desmopressin -- Unigene
 Desmoteplase -- Merck, Schering AG
 Destabilase
 Diabetes gene therapy -- DeveloGen, Pfizer
 Diabetes therapy -- Crucell
 Diabetes type 1 vaccine -- Diamyd
 Therapeutics
 DiaCIM -- YM BioSciences
 dialytic oligopeptides -- Research Corp
 Diamyd -- Diamyd Therapeutics
 DiaPep227 -- Peppen
 DiavaX -- Corixa
 Digoxin MAb -- Glaxo
 Diphtheria tetanus pertussis-hepatitis B
 vaccine -- GlaxoSmithKline
 DIR therapy -- Solis Therapeutics --
 DNase -- Genentech
 Dornase alfa -- Genentech
 Dornase alfa, inhalation -- Genentech
 Doxorubicin-anti-CEA MAb conjugate --
 Immunomedics
 DP-107 -- Trimeris
 drotrecogin alfa -- Eli Lilly
 DTctGMCSF
 DTP-polio vaccine -- Aventis Pasteur
 DU 257-KM231 antibody conjugate --
 Kyowa
 dural graft matrix -- Integra
 Duteplase -- Baxter Intl.
 DWP-401 -- Daewoong
 DWP-404 -- Daewoong
 DWP-408 -- Daewoong
 Dx 88 (Epi-KAL2) -- Dyax
 Dx 890 (elastin inhibitors) -- Dyax
 E coli O157 vaccine -- NIH
 E21-R -- BresaGen
 Eastern equine encephalitis virus vaccine --
 Echicetin --
 Echinhibin 1 --
 Echistatin -- Merck
 Echitamine --
 Ecomeximab -- Kyowa Hakko
 EC-SOD -- PPL Therapeutics
 Eculizumab (5G1.1) -- Alexion
 EDF -- Ajinomoto
 EDN derivative -- NIH
 EDNA -- NIH
 Edobacomab -- XOMA
 Edrecolomab -- Centocor
 EF 5077
 Efalizumab -- Genentech
 EGF fusion toxin -- Seragen, Ligand
 EGF-P64k vaccine -- Center of Molecular
 Immunology
 EL 246 -- LigoCyte
 elastase inhibitor -- Synergen
 elcatonin -- Therapicon
 EMD 72000 -- Merck KGaA
 Emdogain -- BIORA
 emfilmerin -- AMRAD
 Emoctakin -- Novartis
 enamel matrix protein -- BIORA
 Endo III -- NYU
 endostatin -- EntreMed, Pharis
 Enhancins -- Micrologix
 Enlimomab -- Isis Pharm.
 Enoxaparin sodium -- Pharmuka
 enzyme linked antibody nutrient depletion
 therapy -- KS Biomedix Holdings

FIG. 28J

41/497

Eosinophil-derived neutralizing agent – EP-51216 – Asta Medica	Factor VII – Novo Nordisk, Bayer, Baxter Intl.
EP-51389 – Asta Medica	Factor VIIa – PPL Therapeutics, ZymoGenetics
EPH family ligands – Regeneron	Factor VIII – Bayer Genentech, Beaufour-Ipsen, CLB, Inex, Octagen, Pharmacia, Pharming
Epidermal growth factor – Hitachi Kasei, Johnson & Johnson	Factor VIII – PEGylated – Bayer
Epidermal growth factor fusion toxin – Senetek	Factor VIII fragments – Pharmacia
Epidermal growth factor-genistein – EPH-HNE-4 – Dyax	Factor VIII gene therapy – Targeted Genetics
EPH-KAL2 – Dyax	Factor VIII sucrose formulation – Bayer, Genentech
Epoetin-alfa – Amgen, Dragon Pharmaceuticals, Nanjing Huaxin	Factor VIII-2 – Bayer
Eprätuzumab – Immunomedics	Factor VIII-3 – Bayer
Epstein-Barr virus vaccine – Aviron/SmithKline Beecham, Bioresearch	Factor Xa inhibitors – Merck, Novo Nordisk, Mochida
Eptacog alfa – Novo Nordisk	Factor XII – ZymoGenetics
Eptifibatide – COR Therapeutics	Factors VIII and IX gene therapy – Genetics Institute/Targeted Genetics
erb-38 –	Famoxin – Genset
Erlizumab – Genentech	Fas (delta) TM protein – LXR BioTech.
erythropoietin – Alkermes, ProLease, Dong-A, Elanex, Genetics Institute, LG Chem, Protein Sciences, Serono, Snow Brand, SRC VB VECTOR, Transkaryotic Therapies	Fas TR – Human Genome Sciences
Erythropoietin Beta – Hoffman La Roche	Felvizumab – Scotgen
Erythropoietin/Epoetin alfa – Chugai	FFR-VIIa – Novo Nordisk
Escherichia coli vaccine – North American Vaccine, SBL Vaccin, Swiss Serum and Vaccine Institute Berne	FG-001 – F-Gene
etanercept – Immunex	FG-002 – F-Gene
examorelin – Mediolanum	FG-004 – F-Gene
Exendin 4 – Amylin	FG-005 – F-Gene
exonuclease VII	FGF + fibrin – Repair
F 105 – Centocor	Fibrimage – Bio-Tech. General
F-992 – Fornix	fibrin-binding peptides – ISIS Innovation
Factor IX – Alpha Therapeutics, Wellfide Corp., CSL, Genetics Institute/AHP, Pharmacia, PPL Therapeutics	fibrinogen – PPL Therapeutics, Pharming
Factor IX gene therapy – Cell Genesys	fibroblast growth factor – Chiron, NYU, Ramot, ZymoGenetics
	fibrolase conjugate – Schering AG
	Filgrastim – Amgen
	filgrastim – PDA modified – Xencor
	FLT-3 ligand – Immunex
	FN18 CRM9 –

FIG. 28K

42/497

folliculin -- Biotech Australia, Human Therapeutics	glutamate decarboxylase -- Genzyme Transgenics
folliculin alfa -- Alkermes, ProLease, PowderJect, Serono, Akzo Nobel	Glycoprotein S3 -- Kureha
Folliculin Beta -- Bayer, Organon	GM-CSF -- Immunex
FP 59	GM-CSF tumour vaccine -- PowderJect
FSH -- Ferring	GnRH immunotherapeutic -- Protherics
FSH + LH -- Ferring	Goserelin (LhRH antagonist) -- AstraZeneca
F-spondin -- CeNeS	gp75 antigen -- ImClone
fusion protein delivery system -- UAB Research Foundation	gp96 -- Antigenics
fusion toxins -- Boston Life Sciences	GPI 0100 -- Galenica
G 5598 -- Genentech	GR 4991W93 -- GlaxoSmithKline
GA-II -- Transkaryotic Therapies	Granulocyte colony-stimulating factor -- Dong-A
Gamma-interferon analogues -- SRC VB VECTOR	Granulocyte colony-stimulating factor conjugate
Ganirelix -- Roche	grass allergy therapy -- Dynavax
gastric lipase -- Meristem	GRF1-44 -- ICN
Gavilimomab --	Growth Factor -- Chiron, Atrigel, Atrix, Innogenetics, ZymoGenetics, Novo
G-CSF -- Amgen, SRC VB VECTOR	growth factor peptides -- Biotherapeutics
GDF-1 -- CeNeS	growth hormone -- LG Chem
GDF-5 -- Biopharm	growth hormone, Recombinant human -- Serono
GDNF (glial derived neurotrophic factor) -- Amgen	GT 4086 -- Glatech
gelsolin -- Biogen	GW 353430 -- GlaxoSmithKline
Gemtuzumab ozogamicin -- Celltech	GW-278884 -- GlaxoSmithKline
Gene-activated epoetin-alfa -- Aventis Pharma -- Transkaryotic Therapies	H 11 -- Viventia Biotech
Glanzmann thrombasthenia gene therapy --	H5N1 influenza A virus vaccine -- Protein Sciences
Glatiramer acetate -- Yeda	haemoglobin -- Biopure
glial growth factor 2 -- CeNeS	haemoglobin 3011, Recombinant -- Baxter Healthcare
GLP-1 -- Amylin, Suntory, TheraTech, Watson	haemoglobin crosfumaril -- Baxter Intl.
GLP-1 peptide analogues -- Zealand Pharmaceuticals	haemoglobin stabilized -- Ajinomoto
glucagon -- Eli Lilly, ZymoGenetics	haemoglobin, recombinant -- Apex
Glucagon-like peptide-1 7-36 amide -- Suntory	HAF -- Immune Response
Glucocigen-like peptide -- Amylin	Hantavirus vaccine
Glucocerebrosidase -- Genzyme	HB 19
	HBNF -- Regeneron
	HCC-1 -- Pharis
	hCG -- Milkhaus

FIG. 28L

43/497

hCG vaccine -- Zonagen	Herpes simplex glycoprotein DNA vaccine --
HE-317 -- Hollis-Eden Pharmaceuticals	Merck, Wyeth-Lederle Vaccines-Malvern,
Heat shock protein cancer and influenza	Genentech, GlaxoSmithKline, Chiron,
vaccines -- StressGen	Takeda
Helicobacter pylori vaccine -- Acambis,	Herpes simplex vaccine -- Cantab
AstraZeneca/CSL, Chiron, Provalis	Pharmaceuticals, CEL-SCI, Henderson
Helistat-G -- GalaGen	Morley
Hemolink -- Hemosol	Herpes simplex vaccine live -- ImClone
hepapoietin -- Snow Brand	Systems/Wyeth-Lederle, Aventis Pasteur
heparanase -- InSight	HGF derivatives -- Dompe
heparinase I -- Ibex	hIAPP vaccine -- Crucell
heparinase III -- Ibex	Hib-hepatitis B vaccine -- Aventis Pasteur
Hepatitis A vaccine -- American Biogenetic	HIC 1
Sciences	HIP -- Altachem
Hepatitis A vaccine inactivated	Hirudins -- Biopharma, Cangene, Dongkook,
Hepatitis A vaccine Nothav -- Chiron	Japan Energy Corporation, Pharmacia
Hepatitis A-hepatitis B vaccine --	Corporation, SIR International, Sanofi-
GlaxoSmithKline	Synthelabo, Sotragene, Rhein Biotech
hepatitis B therapy -- Tripep	HIV edible vaccine -- ProdiGene
Hepatitis B vaccine -- Amgen, Chiron SpA,	HIV gp120 vaccine -- Chiron, Ajinomoto,
Meiji Milk, NIS, Prodeva, PowderJect,	GlaxoSmithKline, ID Vaccine, Progenics,
Rhein Biotech	VaxGen
Hepatitis B vaccine recombinant -- Evans	HIV gp120 vaccine gene therapy --
Vaccines, Eptec Combiotech, Genentech,	HIV gp160 DNA vaccine -- PowderJect,
MedImmune, Merck Sharp & Dohme,	Aventis Pasteur, Oncogen, Hyland
Rhein Biotech, Shantha Biotechnics,	Immuno, Protein Sciences
Vector, Yeda	HIV gp41 vaccine -- Panacos
Hepatitis B vaccine recombinant TGP 943 --	HIV HGP-30W vaccine -- CEL-SCI
Takeda	HIV immune globulin -- Abbott, Chiron
Hepatitis C vaccine -- Bavarian Nordic,	HIV peptides -- American Home Products
Chiron, Innogenetics Acambis,	HIV vaccine -- Applied bioTech., Axis
Hepatitis D vaccine -- Chiron Vaccines	Genetics, Biogen, Bristol-Myers Squibb,
Hepatitis E vaccine recombinant --	Genentech, Korea Green Cross, NIS,
Genelabs/GlaxoSmithKline, Novavax	Oncogen, Protein Sciences Corporation,
hepatocyte growth factor -- Panorama,	Terumo, Tonen Corporation, Wyeth-
Sosei	Ayerst, Wyeth-Lederle Vaccines-Malvern,
hepatocyte growth factor kringle fragments --	Advanced BioScience Laboratories,
- EntreMed	Bavarian Nordic, Bavarian Nordic/Statens
Her-2/Neu peptides -- Corixa	Serum Institute, GeneCure, Immune
	Response, Progenics, Therion Biologics,
	United Biomedical, Chiron

FIG. 28M

44/497

HIV vaccine vCP1433 -- Aventis Pasteur
 HIV vaccine vCP1452 -- Aventis Pasteur
 HIV vaccine vCP205 -- Aventis Pasteur
 HL-9 -- American BioScience
 HM-9239 -- Cytran
 HML-103 -- Hemosol
 HML-104 -- Hemosol
 HML-105 -- Hemosol
 HML-109 -- Hemosol
 HML-110 -- Hemosol
 HML-121 -- Hemosol
 hNLP -- Pharis
 Hookworm vaccine
 host-vector vaccines -- Henogen
 HPM 1 -- Chugai
 HPV vaccine -- MediGene
 HSA -- Meristem
 HSF -- StressGen
 HSP carriers -- Weizmann, Yeda, Peptor
 HSPPC-70 -- Antigenics
 HSPPC-96, pathogen-derived -- Antigenics
 HSV 863 -- Novartis
 HTLV-I DNA vaccine
 HTLV-I vaccine
 HTLV-II vaccine -- Access
 HU 901 -- Tanox
 Hu23F2G -- ICOS
 HuHMFG1
 HumaLYM -- Intracell
 Human krebs statika -- Yamanouchi
 human monoclonal antibodies --
 Abgenix/Biogen, Abgenix/ Corixa,
 Abgenix/ Immunex, Abgenix/Lexicon,
 Abgenix/ Pfizer, Athersys/Medarex,
 Biogen/MorphoSys, CAT/Searle,
 Centocor/Medarex, Corixa/Kirin Brewery,
 Corixa/Medarex, Eos BioTech/Medarex,
 Eos/Xenex, Exelixis/Protein Design
 Labs, ImmunoGen/ Raven, Medarex/
 B.Twelve, MorphoSys/ImmunoGen, XTL
 Biopharmaceuticals/Dyax,
 Human monoclonal antibodies --
 Medarex/Northwest Biotherapeutics,
 Medarex/Seattle Genetics
 human netrin-1 -- Exelixis
 human papillomavirus antibodies -- Epicyte
 Human papillomavirus vaccine -- Biotech
 Australia, IDEC, StressGen
 Human papillomavirus vaccine MEDI 501 --
 MedImmune/GlaxoSmithKline
 Human papillomavirus vaccine MEDI
 503/MEDI 504 --
 MedImmune/GlaxoSmithKline
 Human papillomavirus vaccine TA-CIN --
 Cantab Pharmaceuticals
 Human papillomavirus vaccine TA-HPV --
 Cantab Pharmaceuticals
 Human papillomavirus vaccine TH-GW --
 Cantab/GlaxoSmithKline
 human polyclonal antibodies -- Biosite/Eos
 BioTech./ Medarex
 human type II anti factor VIII monoclonal
 antibodies -- ThromboGenics
 humanised anti glycoprotein Ib murine
 monoclonal antibodies -- ThromboGenics
 HumaRAD -- Intracell
 HuMax EGFR -- Genmab
 HuMax-CD4 -- Medarex
 HuMax-IL15 -- Genmab
 HYB 190 -- Hybridon
 HYB 676 -- Hybridon
 I-125 MAb A33 -- Celltech
 Ibritumomab tiuxetan -- IDEC
 IBT-9401 -- Ibex
 IBT-9402 -- Ibex
 IC 14 -- ICOS
 Idarubicin anti-Ly-2.1 --
 IDEC 114 -- IDEC
 IDEC 131 -- IDEC
 IDEC 152 -- IDEC
 IDM 1 -- IDM
 IDPS -- Hollis-Eden Pharmaceuticals

FIG. 28N

45/497

iduronate-2-sulfatase -- Transkaryotic Therapies
 IGF/IBP-2-13 -- Pharis
 IGN-101 -- Igeneon
 IK HIR02 -- Iketon
 IL-11 -- Genetics Institute/AHP
 IL-13-PE38 -- NeoPharm
 IL-17 receptor -- Immunex
 IL-18BP -- Yeda
 IL-1Hy1 -- Hyseq
 IL-1 β -- Celltech
 IL-1 β adjuvant -- Celltech
 IL-2 -- Chiron
 IL-2 + IL-12 -- Hoffman La-Roche
 IL-6/sIL-6R fusion -- Hadasit
 IL-6R derivative -- Tosoh
 IL-7-Dap 389 fusion toxin -- Ligand
 IM-862 -- Cytran
 IMC-1C11 -- ImClone
 imiglucerase -- Genzyme
 Immune globulin intravenous (human) -- Hoffman La Roche
 immune privilege factor -- Proneuron
 Immunocal -- Immunotec
 Immunogene therapy -- Briana Bio-Tech
 Immunoliposomal 5-fluorodeoxyuridine-dipalmitate --
 immunosuppressant vaccine -- Aixie
 immunotoxin -- Antisoma, NIH
 ImmuRAIT-Re-188 -- Immunomedics
 imreg-1 -- Imreg
 infertility -- Johnson & Johnson, E-TRANS
 Infliximab -- Centocor
 Influenza virus vaccine -- Aventis Pasteur, Protein Sciences
 inhibit -- Biotech Australia, Human Therapeutics
 Inhibitory G protein gene therapy
 INKP-2001 -- InKine
 Inolimomab -- Diaclone
 insulin -- Autolimmune, Altea, Biobras, BioSante, Bio-Tech. General, Chong Kun Dang, Emisphere, Flamel, Provalis, Rhein Biotech, TranXenoGen
 insulin (bovine) -- Novartis
 insulin analogue -- Eli Lilly
 Insulin Aspart -- Novo Nordisk
 insulin detemir -- Novo Nordisk
 insulin glargine -- Aventis
 insulin inhaled -- Inhale Therapeutics Systems, Alkermes
 insulin oral -- Inovax
 insulin, AeroDose -- AeroGen
 insulin, AERx -- Aradigm
 insulin, BEODAS -- Elan
 insulin, Biphasix -- Helix
 insulin, buccal -- Generex
 insulin, I2R -- Flemington
 insulin, intranasal -- Bentley
 insulin, oral -- Nobex, Unigene
 insulin, Orasome -- Endorex
 insulin, ProMaxx -- Epic
 insulin, Quadrant -- Elan
 insulin, recombinant -- Aventis
 insulin, Spiros -- Elan
 insulin, Transfersome -- IDEA
 insulin, Zymo, recombinant -- Novo Nordisk
 insulintropin -- Scios
 Insulysin gene therapy --
 integrin antagonists -- Merck
 interferon (Alpha2) -- SRC VB VECTOR, Viragen, Dong-A, Hoffman La-Roche, Genentech
 interferon -- BioMedicines, Human Genome Sciences
 interferon (Alfa-n3) -- Interferon Sciences Intl.
 interferon (Alpha), Biphasix -- Helix

FIG. 280

46/497

interferon (Alpha)—Amgen, BioNative,
 Novartis, Genzyme Transgenics,
 Hayashibara, Inhale Therapeutics
 Systems, Medusa, Flamel, Dong-A,
 GeneTrol, Nasteck, Shantha,
 Wassermann, LG Chem, Sumitomo,
 Aventis, Behring EGIS, Pepgen, Servier,
 Rhein Biotech,
 interferon (Alpha2A)
 interferon (Alpha2B) — Enzon, Schering-
 Plough, Biogen, IDEA
 interferon (Alpha-N1) — GlaxoSmithKline
 interferon (beta) — Rentschler, GeneTrol,
 Meristem, Rhein Biotech, Toray, Yeda,
 Daiichi, Mochida
 interferon (Beta1A) — Sero, Biogen
 interferon (beta1A), inhale — Biogen
 interferon (B1b)— Chiron
 interferon (tau)— Pepgen
 Interferon alfacon-1 — Amgen
 Interferon alpha-2a vaccine
 Interferon Beta 1b — Schering/Chiron,
 InterMune
 Interferon Gamma — Boehringer Ingelheim,
 Sheffield, Rentschler, Hayashibara
 interferon receptor, Type I — Sero
 interferon(Gamma1B) — Genentech
 Interferon-alpha-2b + ribavirin — Biogen,
 ICN
 interferon-alpha-2b gene therapy —
 Schering-Plough
 Interferon-con1 gene therapy —
 interleukin-1 antagonists — Dompe
 interleukin-1 receptor antagonist — Abbott
 Bioresearch, Pharmacia
 interleukin-1 receptor type I — Immunex
 interleukin-1 receptor Type II — Immunex
 Interleukin-1 trap — Regeneron
 Interleukin-1-alpha — Immunex/Roche
 interleukin-2 — SRC VB VECTOR,
 Ajinomoto, Biomira, Chiron
 IL-2/ diphtheria toxin — Ligand
 Interleukin-3 — Cangene
 Interleukin-4 — Immunology Ventures,
 Sanofi Winthrop, Schering-Plough,
 Immunex/ Sanofi Winthrop, Bayer, Ono
 interleukin-4 + TNF-Alpha — NIH
 interleukin-4 agonist — Bayer
 interleukin-4 fusion toxin — Ligand
 Interleukin-4 receptor — Immunex, Immun
 Interleukin-6 — Ajinomoto, Cangene, Yeda,
 Genetics Institute, Novartis
 interleukin-6 fusion protein
 Interleukin-6 fusion toxin — Ligand, Sero
 interleukin-7 — IC Innovations
 interleukin-7 receptor — Immunex
 interleukin-8 antagonists — Kyowa
 Hakko/Millennium/Pfizer
 interleukin-9 antagonists — Genaera
 Interleukin-10 — DNAX, Schering-Plough
 Interleukin-10 gene therapy —
 interleukin-12 — Genetics Institute, Hoffman
 La-Roche
 interleukin-13 — Sanofi
 interleukin-13 antagonists — AMRAD
 Interleukin-13-PE38QQR
 interleukin-15 — Immunex
 interleukin-16 — Research Corp
 interleukin-18 — GlaxoSmithKline
 Interleukin-18 binding protein — Sero
 Ior-P3 — Center of Molecular Immunology
 IP-10 — NIH
 IPF — Metabolex
 IR-501 — Immune Response
 ISIS 9125 — Isis Pharmaceuticals
 ISURF No. 1554 — Millennium
 ISURF No. 1866 — Iowa State Univer.
 ITF-1697 — Italfarmaco
 Ix-162 — Ixion
 J 695 — Cambridge Antibody Tech.,
 Genetics Inst., Knoll
 Jagged + FGF — Repair

FIG. 28P

47/497

JKC-362 -- Phoenix Pharmaceuticals
 JTP-2942 -- Japan Tobacco
 Juman monoclonal antibodies -- Medarex/Raven
 K02 -- Axys Pharmaceuticals
 Kelliximab -- IDEC
 Keyhole limpet haemocyanin
 KGF -- Amgen
 KM 871 -- Kyowa
 KPI 135 -- Scios
 KPI-022 -- Scios
 Kringle 5
 KSB 304
 KSB-201 -- KS Biomedix
 L 696418 -- Merck
 L 703801 -- Merck
 L1 -- Acorda
 L-761191 -- Merck
 lactoferrin -- Meristem, Pharming, Agennix
 lactoferrin cardio -- Pharming
 LAG-3 -- Serono
 LAIT -- GEMMA
 LAK cell cytotoxin -- Arizona
 lamellarins -- PharmaMar/University of Malaga
 laminin A peptides -- NIH
 lanotepase -- Genetics Institute
 laronidase -- BioMarin
 Lassa fever vaccine
 LCAT -- NIH
 LDP 01 -- Millennium
 LDP 02 -- Millennium
 Lecithinized superoxide dismutase -- Seikagaku
 LeIF adjuvant -- Corixa
 leishmaniasis vaccine -- Corixa
 lenercept -- Hoffman La-Roche
 Lenograstim -- Aventis, Chugai
 lepirudin -- Aventis
 leptin -- Amgen, IC Innovations
 Leptin gene therapy -- Chiron Corporation
 leptin, 2nd-generation -- Amgen
 leridistim -- Pharmacia
 leuprolide, ProMaxx -- Epic
 leuporellin, oral -- Unigene
 LeuTech -- Papatin
 LEX 032 -- SuperGen
 LIDEPT -- Novartis
 Lintuzumab (anti-CD33 MAb) -- Protein Design Labs
 lipase -- Altus Biologics
 lipid A vaccine -- EntreMed
 lipid-linked anchor Tech. -- ICRT, ID Biomedical
 liposome-CD4 Tech. -- Sheffield
 Listeria monocytogenes vaccine
 LMB 1
 LMB 7
 LMB 9 -- Battelle Memorial Institute, NIH
 LM-CD45 -- Cantab Pharmaceuticals
 lovastatin -- Merck
 LSA-3
 LT-B receptor -- Biogen
 lung cancer vaccine -- Corixa
 lusupultide -- Scios
 L-Vax -- AVAX
 LY 355455 -- Eli Lilly
 LY 366405 -- Eli Lilly
 LY-355101 -- Eli Lilly
 Lyme disease DNA vaccine -- Vical/Aventis Pasteur
 Lyme disease vaccine -- Aquila
 Biopharmaceuticals, Aventis, Pasteur, Symbicom, GlaxoSmithKline, Hyland
 Immuno, MedImmune
 Lymphocytic choriomeningitis virus vaccine
 lymphoma vaccine -- Biomira, Genitope
 LYP18
 lys plasminogen, recombinant
 Lysosomal storage disease gene therapy -- Avigen
 lysostaphin -- Nutrition 21

FIG. 28Q

48/497

M 23 -- Gruenenthal
 M1 monoclonal antibodies -- Acorda
 Therapeutics
 MA 16N7C2 -- Corvas Intl.
 malaria vaccine -- GlaxoSmithKline,
 AdProTech, Antigenics, Apovia, Aventis
 Pasteur, Axis Genetics, Behringwerke,
 CDCP, Chiron Vaccines, Genzyme
 Transgenics, Hawaii, MedImmune, NIH,
 NYU, Oxxon, Roche/Saramane, Biotech
 Australia, Rx Tech
 Malaria vaccine CDC/NIIMALVAC-1
 malaria vaccine, multicomponent
 mammaglobin -- Corixa
 mammatatin -- Biotherapeutics
 mannan-binding lectin -- NatlImmu
 mannan-MUC1 -- Psiron
 MAP 30
 Marinovir -- Phytera
 MARstem -- Maret
 MB-015 -- Mochida
 MBP -- ImmuLogic
 MCI-028 -- Mitsubishi-Tokyo
 MCIF -- Human Genome Sciences
 MDC -- Advanced BioScience -- Akzo
 Nobel, ICOS
 MDX 11 -- Medarex
 MDX 210 -- Medarex
 MDX 22 -- Medarex
 MDX 22
 MDX 240 -- Medarex
 MDX 33
 MDX 44 -- Medarex
 MDX 447 -- Medarex
 MDX H210 -- Medarex
 MDX RA -- Houston BioTech., Medarex
 ME-104 -- Pharmexa
 Measles vaccine
 Mecasermin -- Cephalon/Chiron; Chiron
 MEDI 488 -- MedImmune
 MEDI 500
 MEDI 507 -- BioTransplant
 melanin concentrating hormone --
 Neurocrine Biosciences
 melanocortins -- OMRF
 Melanoma monoclonal antibodies -- Viragen
 melanoma vaccine -- GlaxoSmithKline,
 Akzo Nobel, Avant, Aventis Pasteur,
 Bavarian Nordic, Biovector, CancerVax,
 Genzyme Molecular Oncology, Humbolt,
 ImClone Systems, Memorial, NYU, Oxxon
 Melanoma vaccine Magevac -- Therion
 memory enhancers -- Scios
 meningococcal B vaccine -- Chiron
 meningococcal vaccine -- CAMR
 Meningococcal vaccine group B conjugate -
 - North American Vaccine
 Meningococcal vaccine group B
 recombinant -- BioChem Vaccines,
 Microscience
 Meningococcal vaccine group Y conjugate -
 - North American Vaccine
 Meningococcal vaccine groups A B and C
 conjugate -- North American Vaccine
 Mepolizumab -- GlaxoSmithKline
 Metastatin -- EntreMed, Takeda
 Met-CkB7 -- Human Genome Sciences
 met-enkephalin -- TNI
 METH-1 -- Human Genome Sciences
 methioninase -- AntiCancer
 Methionine lyase gene therapy --
 AntiCancer
 Met-RANTES -- Genexa Biomedical,
 Serono
 Metreleptin
 Microtubule inhibitor MAB
 Immunogen/Abgenix
 MGDF -- Kirin
 MGTV -- Progenics
 micrin -- Endocrine
 microplasmin -- ThromboGenics
 MIF -- Genetics Institute

FIG. 28R

49/497

migration inhibitory factor -- NIH	MAb 45-2D9 -- haematoporphyrin conjugate
Mim CD4.1 -- Xyte Therapies	MAb 4B4
mirostipen -- Human Genome Sciences	MAb 4E3-CPA conjugate -- BCM Oncologia
Mitumomab (BEC-2) -- ImClone Systems, Merck KGaA	MAb 4E3-daunorubicin conjugate
MK 852 -- Merck	MAb 50-6
MLN 1202 (Anti-CCR2 monoclonal antibody) -- Millenium Pharmaceuticals	MAb 50-61A -- Institut Pasteur
Mobenakin -- NIS	MAb 5A8 -- Biogen
molgramostim -- Genetics Institute, Novartis	MAb 791T/36-methotrexate conjugate
monoclonal antibodies -- Abgenix/Celltech, Immusol/ Medarex, Viragen/ Roslin Institute, Cambridge Antibody Tech./Elan	MAb 7c11.e8
MAb 108 --	MAb 7E11 C5-selenocystamine conjugate
MAb 10D5 --	MAb 93KA9 -- Novartis
MAb 14.18-interleukin-2 immunocytokine -- Lexigen	MAb A5B7-cisplatin conjugate -- Biodynamics Research, Pharmacia
MAb 14G2a --	MAb A5B7-I-131
MAb 15A10 --	MAb A7
MAb 170 -- Biomira	MAb A717 -- Exocell
MAb 177Lu CC49 --	MAb A7-zinostatin conjugate
MAb 17F9	MAb ABX-RB2 -- Abgenix
MAb 1D7	MAb ACA 11
MAb 1F7 -- Immune Network	MAb AFP-I-131 -- Immunomedics
MAb 1H10-doxorubicin conjugate	MAb AP1
MAb 26-2F	MAb AZ1
MAb 2A11	MAb B3-LysPE40 conjugate
MAb 2E1 -- RW Johnson	MAb B4 -- United Biomedical
MAb 2F5	MAb B43 Genistein-conjugate
MAb 31.1 -- International BioImmune Systems	MAb B43.13-Tc-99m -- Biomira
MAb 32 -- Cambridge Antibody Tech., Peptech	MAb B43-PAP conjugate
MAb 323A3 -- Centocor	MAb B4G7-gelonin conjugate
MAb 3C5	MAb BCM 43-daunorubicin conjugate -- BCM Oncologia
MAb 3F12	MAb BIS-1
MAb 3F8	MAb BMS 181170 -- Bristol-Myers Squibb
MAb 42/6	MAb BR55-2
MAb 425 -- Merck KGaA	MAb BW494
MAb 447-52D -- Merck Sharp & Dohme	MAb C 242-DM1 conjugate -- ImmunoGen
	MAb C242-PE conjugate
	MAb c30-6
	MAb CA208-cytorhodin-S conjugate -- Hoechst Japan
	MAb CC49 -- Enzo

FIG. 28S

50/497

MAb ch14.18 --	MAb LL2-I-131 -- Immunomedics
MAb CH14.18-GM-CSF fusion protein -- Lexigen	MAb LL2-Y-90
MAB chCE7	MAB LS2D617 -- Hybritech
MAB CI-137 -- AMRAD	MAB LYM-1-gelonin conjugate
MAB cisplatin conjugate	MAB LYM-1-I-131
MAB CLB-CD19	MAB LYM-1-Y-90
MAB CLB-CD19v	MAB LYM-2 -- Peregrine
MAB CLL-1 -- Peregrine	MAB M195
MAB CLL-1-GM-CSF conjugate	MAB M195-bismuth 213 conjugate -- Protein Design Labs
MAB CLL-1-IL-2 conjugate -- Peregrine	MAB M195-gelonin conjugate
MAB CLN IgG -- doxorubicin conjugates	MAB M195-I-131
MAB conjugates -- Tanox	MAB M195-Y-90
MAB D612	MAB MA 33H1 -- Sanofi
MAB Dal B02	MAB MAD11
MAB DC101 -- ImClone	MAB MGB2
MAB EA 1 --	MAB MINT5
MAB EC708 -- Biovation	MAB MK2-23
MAB EP-5C7 -- Protein Design Labs	MAB MOC31 ETA(252-613) conjugate
MAB ERIC-1 -- ICRT	MAB MOC-31-In-111
MAB F105 gene therapy	MAB MOC-31-PE conjugate
MAB FC 2.15	MAB MR6 --
MAB G250 -- Centocor	MAB MRK-16 -- Aventis Pasteur
MAB GA6	MAB MS11G6
MAB GA733	MAB MX-DTPA BrE-3
MAB Gilomab-H -- Viventia Biotech	MAB MY9
MAB HB2-saporin conjugate	MAB Nd2 -- Tosoh
MAB HD 37 --	MAB NG-1 -- Hygeia
MAB HD37-ricin chain-A conjugate	MAB NM01 -- Nissin Food
MAB HNK20 -- Acambis	MAB OC 125
MAB huN901-DM1 conjugate -- ImmunoGen	MAB OC 125-CMA conjugate
MAB I-131 CC49 -- Corixa	MAB OKI-1 -- Ortho-McNeil
MAB ICO25	MAB OX52 -- Bioproducts for Science
MAB ICR12-CPG2 conjugate	MAB PMA5
MAB ICR-62	MAB PR1
MAB IRac-ricin A conjugate	MAB prost 30
MAB K1	MAB R-24
MAB KS1-4-methotrexate conjugate	MAB R-24 α Human GD3 -- Celltech
MAB L6 -- Bristol-Myers Squibb, Oncogen	MAB RFB4-ricin chain A conjugate
MAB LICO 16-88	MAB RFT5-ricin chain A conjugate
	MAB SC 1

FIG. 28T

51/497

MAb SM-3 -- ICRT
 MAb SMART 1D10 -- Protein Design Labs
 MAb SMART ABL 364 -- Novartis
 MAb SN6f
 MAb SN6f-deglycosylated ricin A chain conjugate --
 MAb SN6j
 MAb SN7-ricin chain A conjugate
 MAb T101-Y-90 conjugate -- Hybritech
 MAb T-88 -- Chiron
 MAb TB94 -- Cancer ImmunoBiology
 MAb TEC 11
 MAb TES-23 -- Chugai
 MAb TM31 -- Avant
 MAb TNT-1 -- Cambridge Antibody Tech.,
 Peregrine
 MAb TNT-3
 MAb TNT-3 -- IL2 fusion protein --
 MAb TP3-At-211
 MAb TP3-PAP conjugate --
 MAb UJ13A -- ICRT
 MAb UN3
 MAb ZME-018-gelonin conjugate
 MAb-BC2 -- GlaxoSmithKline
 MAb-DM1 conjugate -- ImmunoGen
 MAb-ricin-chain-A conjugate -- XOMA
 MAb-temoporfin conjugates
 Monopharm C -- Viventia Biotech
 monteplase -- Eisai
 montirelin hydrate -- Gruenthal
 moroctocog alfa -- Genetics Institute
 Moroctocog-alfa -- Pharmacia
 MP 4
 MP-121 -- Biopharm
 MP-52 -- Biopharm
 MRA -- Chugai
 MS 28168 -- Mitsui Chemicals, Nihon
 Schering
 MSH fusion toxin -- Ligand
 MSI-99 -- Genaera
 MT 201 -- Micromet
 Muc-1 vaccine -- Corixa
 mucosal tolerance -- Aberdeen
 mullerian inhibiting subst
 muplestim -- Genetics Institute, Novartis,
 DSM Anti-Infectives
 murine MAb -- KS Biomedix
 Mutant somatropin -- JCR Pharmaceutical
 MV 833 -- Toagosei
 Mycoplasma pulmonis vaccine
 Mycoprex -- XOMA
 myeloperoxidase -- Henogen
 myostatin -- Genetics Institute
 Nacolumab tafenoxy -- Pharmacia
 Nagrecor -- Scios
 nagrestipen -- British Biotech
 NAP-5 -- Corvas Intl.
 NAPc2 -- Corvas Intl.
 nartogastim -- Kyowa
 Natalizumab -- Protein Design Labs
 Nateplase -- NIH, Nihon Schering
 nateplase -- Schering AG
 NBI-3001 -- Neurocrine Biosci.
 NBI-5788 -- Neurocrine Biosci.
 NBI-6024 -- Neurocrine Biosci.
 Nef inhibitors -- BRI
 Neisseria gonorrhoea vaccine -- Antex
 Biologics
 Neomycin B-arginine conjugate
 Nerelimomab -- Chiron
 Nerve growth factor -- Amgen -- Chiron,
 Genentech
 Nerve growth factor gene therapy
 nesiritide citrate -- Scios
 neuregulin-2 -- CeNeS
 neurocan -- NYU
 neuronal delivery system -- CAMR
 Neurophil inhibitory Factor -- Corvas
 Neuroprotective vaccine -- University of
 Auckland
 neurotrophic chimaeras -- Regeneron
 neurotrophic factor -- NsGene, CereMedix

FIG. 28U

52/497

NeuroVax -- Immune Response	Oncophage -- Antigenics
neurturin -- Genentech	Oncostatin M -- Bristol-Myers Squibb
neutral endopeptidase -- Genentech	OncoVax-CL -- Jenner Biotherapies
NGF enhancers -- NeuroSearch	OncoVax-P -- Jenner Biotherapies
NHL vaccine -- Large Scale Biology	onercept -- Yeda
NIP45 -- Boston Life Sciences	onychomycosis vaccine -- Boehringer
NKI-B20	Ingelheim
NM 01 -- Nissin Food	opebecan -- XOMA
NMI-139 -- NitroMed	opioids -- Arizona
NMMP -- Genetics Institute	Oprelvekin -- Genetics Institute
NN-2211 -- Novo Nordisk	Oregovomab -- AltaRex
Noggin -- Regeneron	Org-33408 b -- Akzo Nobel
Nonacog alfa	Orlip DP -- EpiCept
Norelin -- Biostar	oryzacycstatin
Norwalk virus vaccine	OSA peptides -- GenSci Regeneration
NRLU 10 -- NeoRx	osteoblast-cadherin GF -- Pharis
NRLU 10 PE -- NeoRx	Osteocalcin-thymidine kinase gene therapy
NT-3 -- Regeneron	osteogenic protein -- Curis
NT-4/5 -- Genentech	osteopontin -- OraPharma
NU 3056	osteoporosis peptides -- Integra, Telios
NU 3076	osteoprotegerin -- Amgen, SnowBrand
NX 1838 -- Gilead Sciences	otitis media vaccines -- Antex Biologics
NY ESO-1/CAG-3 antigen -- NIH	ovarian cancer -- University of Alabama
NYVAC-7 -- Aventis Pasteur	OX40-igG fusion protein -- Cantab, Xenova
NZ-1002 -- Novazyme	P 246 -- Diatide
obesity therapy -- Nobex	P 30 -- Alfacell
OC 10426 -- Ontogen	p1025 -- Active Biotech
OC 144093 -- Ontogen	P-113 ^A -- Demegen
OCIF -- Sankyo	P-16 peptide -- Transition Therapeutics
Oct-43 -- Otsuka	p43 -- Ramot
Odulimomab -- Immunotech	P-50 peptide -- Transition Therapeutics
OK PSA - liposomal	p53 + RAS vaccine -- NIH, NCI
OKT3-gamma-1-ala-ala	PACAP(1-27) analogue
OM 991	paediatric vaccines -- Chiron
OM 992	Pafase -- ICOS
Omalizumab -- Genentech	PAGE-4 plasmid DNA -- IDEC
oncoimmunin-L -- NIH	PAI-2 -- Biotech Australia, Human
Oncolysin B -- ImmunoGen	Therapeutics
Oncolysin CD6 -- ImmunoGen	Palifermin (keratinocyte growth factor) --
Oncolysin M -- ImmunoGen	Amgen
Oncolysin S -- ImmunoGen	Palivizumab -- MedImmune

FIG. 28V

53/497

PAM 4 -- Merck	PEG-uricase -- Mountain View
paniteplase -- Yamanouchi	Pegvisomant -- Genentech
pancreatin, Minitabs -- Eurand	PEGylated proteins, PolyMASC -- Valentis
Pangen -- Fournier	PEGylated recombinant native human leptin
Pantarin -- Selective Genetics	-- Roche
Parainfluenza virus vaccine -- Pharmacia,	Pemtumomab
Pierre Fabre	Penetratin -- Cyclacel
paraoxanase -- Esperion	Pepscan -- Antisoma
parathyroid hormone -- Abiogen, Korea	peptide G -- Peptech, ICRT
Green Cross	peptide vaccine -- NIH, NCI
Parathyroid hormone (1-34) --	Pexelizumab
Chugai/Suntory	pexiganan acetate -- Genaera
Parkinson's disease gene therapy -- Cell	Pharmaprojects No. 3179 -- NYU
Genesys/ Ceregene	Pharmaprojects No. 3390 -- Ernest Orlando
Parvovirus vaccine -- MedImmune	Pharmaprojects No. 3417 -- Sumitomo
PCP-Scan -- Immunomedics	Pharmaprojects No. 3777 -- Acambis
PDGF -- Chiron	Pharmaprojects No. 4209 -- XOMA
PDGF cocktail -- Theratechnologies	Pharmaprojects No. 4349 -- Baxter Intl.
peanut allergy therapy -- Dynavax	Pharmaprojects No. 4651
PEG anti-ICAM MAb -- Boehringer	Pharmaprojects No. 4915 -- Avanir
Ingelheim	Pharmaprojects No. 5156 -- Rhizogenics
PEG asparaginase -- Enzon	Pharmaprojects No. 5200 -- Pfizer
PEG glucocerebrosidase	Pharmaprojects No. 5215 -- Origene
PEG hirudin -- Knoll	Pharmaprojects No. 5216 -- Origene
PEG interferon-alpha-2a -- Roche	Pharmaprojects No. 5218 -- Origene
PEG interferon-alpha-2b + ribavirin --	Pharmaprojects No. 5267 -- ML
Biogen, Enzon, ICN Pharmaceuticals,	Laboratories
Schering-Plough	Pharmaprojects No. 5373 -- MorphoSys
PEG MAb A5B7 --	Pharmaprojects No. 5493 -- Metabolex
Pegacastim -- Amgen -- Kirin Brewery --	Pharmaprojects No. 5707 -- Genentech
ZymoGenetics	Pharmaprojects No. 5728 -- Autogen
Pegaldesleukin -- Research Corp	Pharmaprojects No. 5733 -- BioMarin
pegaspargase -- Enzon	Pharmaprojects No. 5757 -- NIH
pegfilgrastim -- Amgen	Pharmaprojects No. 5765 -- Gryphon
PEG-interferon Alpha -- Viragen	Pharmaprojects No. 5830 -- AntiCancer
PEG-interferon Alpha 2A -- Hoffman La-	Pharmaprojects No. 5839 -- Dyax
Roche	Pharmaprojects No. 5849 -- Johnson &
PEG-interferon Alpha 2B -- Schering-	Johnson
Plough	Pharmaprojects No. 5860 -- Mitsubishi-
PEG-r-hirudin -- Abbott	Tokyo
PEG-rHuMGDF -- Amgen	

FIG. 28W

54/497

Pharmaprojects No. 5869 -- Oxford GlycoSciences	Plasminogen activators -- Abbott Laboratories, American Home Products,
Pharmaprojects No. 5883 -- Asahi Brewery	Boehringer Mannheim, Chiron
Pharmaprojects No. 5947 -- StressGen	Corporation, DuPont Pharmaceuticals, Eli
Pharmaprojects No. 5961 -- Theratechnologies	Lilly, Shionogi, Genentech, Genetics
Pharmaprojects No. 5962 -- NIH	Institute, GlaxoSmithKline, Hemisphere
Pharmaprojects No. 5966 -- NIH	Biopharma, Merck & Co, Novartis,
Pharmaprojects No. 5994 -- Pharming	Pharmacia Corporation, Wakamoto, Yeda
Pharmaprojects No. 5995 -- Pharming	plasminogen-related peptides -- Bio-Tech.
Pharmaprojects No. 6023 -- IMMUCON	General/MGH
Pharmaprojects No. 6063 -- Cytoclonal	platelet factor 4 -- RepliGen
Pharmaprojects No. 6073 -- SIDDCO	Platelet-derived growth factor -- Amgen --
Pharmaprojects No. 6115 -- Genzyme	ZymoGenetics
Pharmaprojects No. 6227 -- NIH	plusonemin-- Hayashibara
Pharmaprojects No. 6230 -- NIH	PMD-2850 -- Protherics
Pharmaprojects No. 6236 -- NIH	Pneumococcal vaccine -- Antex Biologics,
Pharmaprojects No. 6243 -- NIH	Aventis Pasteur
Pharmaprojects No. 6244 -- NIH	Pneumococcal vaccine intranasal --
Pharmaprojects No. 6281 -- Senetek	BioChem Vaccines/Biovector
Pharmaprojects No. 6365 -- NIH	PR1A3
Pharmaprojects No. 6368 -- NIH	PR-39
Pharmaprojects No. 6373 -- NIH	pralmorelin -- Kaken
Pharmaprojects No. 6408 -- Pan Pacific	Pretarget-Lymphoma -- NeoRx
Pharmaprojects No. 6410 -- Athersys	Priliximab -- Centocor
Pharmaprojects No. 6421 -- Oxford GlycoSciences	PRO 140 -- Progenics
Pharmaprojects No. 6522 -- Maxygen	PRO 2000 -- Procept
Pharmaprojects No. 6523 -- Pharis	PRO 367 -- Progenics
Pharmaprojects No. 6538 -- Maxygen	PRO 542 -- Progenics
Pharmaprojects No. 6554 -- APALEXO	pro-Apo A-I -- Esperion
Pharmaprojects No. 6560 -- Ardana	prolactin -- Genzyme
Pharmaprojects No. 6562 -- Bayer	Prosaptide TX14(A) -- Bio-Tech. General
Pharmaprojects No. 6569 -- Eos	prostate cancer antibodies -- Immunex,
Phenoxazine	UroCor
Phenylase -- Ibex	prostate cancer antibody therapy --
Pigment epithelium derived factor --	Genentech/UroGenesys,
plasminogen activator inhibitor-1,	Genotherapeutics
recombinant -- DuPont Pharmaceuticals	prostate cancer immunotherapeutics -- The
	PSMA Development Company
	prostate cancer vaccine -- Aventis Pasteur,
	Zonagen, Corixa, Dendreon, Jenner
	Biotherapies, Therion Biologics

FIG. 28X

55/497

prostate-specific antigen -- EntreMed	RD 62198
protein A -- RepliGen	rDnase -- Genentech
protein adhesives -- Enzon	RDP-58 -- SangStat
protein C -- Baxter Intl., PPL Therapeutics, ZymoGenetics	RecepTox-Fce -- Keryx
protein C activator -- Gilead Sciences	RecepTox-GnRH -- Keryx, MTR Technologies
protein kinase R antagonists -- NIH	RecepTox-MBP -- Keryx, MTR Technologies
protirelin -- Takeda	recFSH -- Akzo Nobel, Organon
protocadherin 2 -- Caprion	REGA 3G12
Pro-urokinase -- Abbott, Bristol-Myers	Regavirumab -- Teijin
Squibb, Dainippon, Tosoh -- Welfide	relaxin -- Connetics Corp
P-selectin glycoprotein ligand-1 -- Genetics Institute	Renal cancer vaccine -- Macropharm
pseudomonas infections -- InterMune	repifermin -- Human Genome Sciences
Pseudomonas vaccine -- CytoVax	Respiratory syncytial virus PFP-2 vaccine -- Wyeth-Lederle
PSGL-Ig -- American Home Products	Respiratory syncytial virus vaccine -- GlaxoSmithKline, Pharmacia, Pierre Fabre
PSP-94 -- Procyon	Respiratory syncytial virus vaccine Inactivated
PTH 1-34 -- Nobex	Respiratory syncytial virus-parainfluenza virus vaccine -- Aventis Pasteur, Pharmacia
Quilimmune-M -- Antigenics	Reteplase -- Boehringer Mannheim, Hoffman La-Roche
R 744 -- Roche	Retropep -- Retroscreen
R 101933	RFB4 (dsFv) PE38
R 125224 -- Sankyo	RFI 641 -- American Home Products
RA therapy -- Cardion	RFTS -- UAB Research Foundation
Rabies vaccine recombinant -- Aventis Pasteur, BioChem Vaccines, Kaketsuken Pharmaceuticals	RG 12986 -- Aventis Pasteur
RadioTheraCIM -- YM BioSciences	RG 83852 -- Aventis Pasteur
Ramot project No. 1315 -- Ramot	RG-1059 -- RepliGen
Ramot project No. K-734A -- Ramot	rGCR -- NIH
Ramot project No. K-734B -- Ramot	rGLP-1 -- Restoragen
Ranibizumab (Anti-VEGF fragment) -- Genentech	rGRF -- Restoragen
RANK -- Immunex	rh Insulin -- Eli Lilly
ranpirase -- Alfacell	RHAMM targeting peptides -- Cangene
ranpirase-anti-CD22 MAb -- Alfacell	rHb1.1 -- Baxter Intl.
RANTES inhibitor -- Milan	rhCC10 -- Claragen
RAPID drug delivery systems -- ARIAD	rhCG -- Sero
rasburicase -- Sanofi	Rheumatoid arthritis gene therapy
rBPI-21, topical -- XOMA	
RC 529 -- Corixa	
rcFTR -- Genzyme Transgenics	

FIG. 28Y

56/497

Rheumatoid arthritis vaccine -- Veterans Affairs Medical Center
 rhLH -- Serono
 Ribozyme gene therapy -- Genset
 Rickettsial vaccine recombinant
 RIGScan CR -- Neoprobe
 RIP-3 -- Rigel
 Rituximab -- Genentech
 RK-0202 -- RxKinetix
 RLT peptide -- Esperion
 rMNEI -- IVAX
 rmCRP -- Immtech
 RN-1001 -- Renovo
 RN-3 -- Renovo
 RNase conjugate -- Immunomedics
 RO 631908 -- Roche
 Rotavirus vaccine -- Merck
 RP 431 -- DuPont Pharmaceuticals
 RP-128 -- Resolution
 RPE65 gene therapy --
 RPR 110173 -- Aventis Pasteur
 RPR 115135 -- Aventis Pasteur
 RPR 116258A -- Aventis Pasteur
 rPSGL-Ig -- American Home Products
 r-SPC surfactant -- Byk Gulden
 RSV antibody -- Medimmune
 Ruplizumab -- Biogen
 rV-HER-2/neu -- Therion Biologics
 SA 1042 -- Sankyo
 sacrosidase -- Orphan Medical
 Sant 7
 Sargramostim -- Immunex
 saruplase -- Gruenenthal
 Satumomab -- Cytogen
 SB 1 -- COR Therapeutics
 SB 207448 -- GlaxoSmithKline
 SB 208651 -- GlaxoSmithKline
 SB 240683 -- GlaxoSmithKline
 SB 249415 -- GlaxoSmithKline
 SB 249417 -- GlaxoSmithKline
 SB 6 -- COR Therapeutics
 SB RA 31012 --
 SC 56929 -- Pharmacia
 SCA binding proteins -- Curis, Enzon
 scFv(14E1)-ETA Berlex Laboratories,
 Schering AG
 ScFv(FRP5)-ETA --
 ScFv6C6-PE40 --
 SCH 55700 -- Celltech
 Schistosomiasis vaccine -- Glaxo
 Wellcome/Medeva, Brazil
 SCPF -- Advanced Tissue Sciences
 scuPA-suPAR complex -- Hadasit
 SD-9427 -- Pharmacia
 SDF-1 -- Ono
 SDZ 215918 -- Novartis
 SDZ 280125 -- Novartis
 SDZ 89104 -- Novartis
 SDZ ABL 364 -- Novartis
 SDZ MMA 383 -- Novartis
 Secretin -- Ferring, Repligen
 serine protease inhbs -- Pharlis
 sermorelin acetate -- Serono
 SERP-1 -- Viron
 sertenef -- Dainippon
 serum albumin, Recombinant human --
 Aventis Behring
 serum-derived factor -- Hadasit
 Sevirumab -- Novartis
 SGN 14 -- Seattle Genetics
 SGN 15 -- Seattle Genetics
 SGN 17/19 -- Seattle Genetics
 SGN 30 -- Seattle Genetics
 SGN-10 -- Seattle Genetics
 SGN-11 -- Seattle Genetics
 SH 306 -- DuPont Pharmaceuticals
 Shanvac-B -- Shantha
 Shigella flexneri vaccine -- Avant, Acambis,
 Novavax
 Shigella sonnei vaccine --
 sICAM-1 -- Boehringer Ingelheim
 Silteplase -- Genzyme

FIG. 28Z

57/497

SIV vaccine -- Endocon, Institut Pasteur
 SK 896 -- Sanwa Kagaku Kenkyusho
 SK-827 -- Sanwa Kagaku Kenkyusho
 Skeleton -- CellFactors
 SKF 106160 -- GlaxoSmithKline
 S-nitroso-AR545C --
 SNTP -- Active Biotech
 somatostatin-1 -- GroPep, Mitsubishi-
 Tokyo, NIH
 somatostatin-1 carrier protein -- Insmed
 somatostatin -- Ferring
 Somatotropin/
 Human Growth Hormone -- Bio-Tech.
 General, Eli Lilly
 somatotropin -- Bio-Tech. General, Alkermes,
 ProLease, Aventis Behring, Biovector,
 Cangene, Dong-A, Eli Lilly, Emisphere,
 Enact, Genentech, Genzyme Transgenics,
 Grandis/Infimed, CSL, Infimed, MacroMed,
 Novartis, Novo Nordisk, Pharmacia
 SeroGen, TranXenoGen
 somatotropin derivative -- Schering AG
 somatotropin, AIR -- Eli Lilly
 Somatotropin, inhaled -- Eli Lilly/Alkermes
 somatotropin, Kabl -- Pharmacia
 somatotropin, Orasome -- Novo Nordisk
 Sonermin -- Dainippon Pharmaceutical
 SP(V5.2)C -- Supertek
 SPf66
 sphingomyelinase -- Genzyme
 SR 29001 -- Sanofi
 SR 41476 -- Sanofi
 SR-29001 -- Sanofi
 SS1(dsFV)-PE38 -- NeoPharm
 β 2 microglobulin -- Avidex
 β 2-microglobulin fusion proteins -- NIH
 β -amyloid peptides -- CeNeS
 β -defensin -- Pharis
 Staphylococcus aureus infections --
 Inhibitex/ZLB
 Staphylococcus aureus vaccine conjugate --
 Nabi
 Staphylococcus therapy -- Tripep
 Staphylokinase -- Biovation, Prothera,
 Thrombogenetics
 Streptococcal A vaccine -- M6
 Pharmaceuticals, North American Vaccine
 Streptococcal B vaccine -- Microscience
 Streptococcal B vaccine recombinant --
 Biochem Vaccines
 Streptococcus pyogenes vaccine
 STRL-33 -- NIH
 Subalin -- SRC VB VECTOR
 SUI5 -- United Biomedical
 SUI5-LHRH -- United Biomedical
 SUN-E3001 -- Suntory
 super high affinity monoclonal antibodies --
 YM BioSciences
 Grandis/Infimed, CSL, Infimed, MacroMed,
 Ube Industries, Bio-Tech, Yeda
 superoxide dismutase-2 -- OXIS
 suppressin -- UAB Research Foundation
 SY-161-P5 -- ThromboGenics
 SY-162 -- ThromboGenics
 Systemic lupus erythematosus vaccine --
 MedClone/VivoRx
 T cell receptor peptides -- Xoma
 T cell receptor peptide vaccine
 T4N5 liposomes -- AGI Dermatics
 TAC1, soluble -- ZymoGenetics
 targeted apoptosis -- Antisoma
 tasonermin -- Boehringer Ingelheim
 TASP
 TASP-V
 Tat peptide analogues -- NIH
 TBP I -- Yeda
 TBP II
 TBV25H -- NIH
 Tc 99m for cea1 -- Center of Molecular
 Immunology
 Tc 99m P 748 -- Diatide

FIG. 28AA

58/497

Tc 99m votumumab -- Intracell	Tissue factor -- Genentech
Tc-99m rh-Annexin V -- Theseus Imaging	Tissue factor pathway inhibitor
teceleukin -- Biogen	TJN-135 -- Tsumura
tenecteplase -- Genentech	TM 27 -- Avant
Teriparatide -- Armour Pharmaceuticals,	TM 29 -- Avant
Asahi Kasei, Eli Lilly	TMC-151 -- Tanabe Seiyaku
terlipressin -- Ferring	TNF tumour necrosis factor -- Asahi Kasei
testisin -- AMRAD	TNF Alpha -- Cytimmune
Tetrafibricin -- Roche	TNF antibody -- Johnson & Johnson
TFPI -- EntreMed	TNF binding protein -- Amgen
tgD-IL-2 -- Takeda	TNF degradation product -- Oncotech
TGF-Alpha -- ZymoGenetics	TNF receptor -- Immunex
TGF- β -- Kolon	TNF receptor 1; soluble -- Amgen
TGF- β 2 -- Insmed	TNF Tumour necrosis factor-alpha -- Asahi
TGF- β 3 -- OSI	Kasei, Genentech, Mochida
Thalassaemia gene therapy -- Crucell	TNF-Alpha Inhibitor -- Tripep
TheraCIM-h-R3 -- Center of Molecular	TNFR:Fc gene therapy -- Targeted Genetics
Immunology, YM BioSciences	TNF-SAM2
Theradigm-HBV -- Epimmune	ToleriMab -- Innogenetics
Theradigm-HPV -- Epimmune	Toxoplasma gondii vaccine --
Theradigm-malaria -- Epimmune	GlaxoSmithKline
Theradigm-melanoma -- Epimmune	TP 9201 -- Telios
TheraFab -- Antisoma	TP10 -- Avant
ThGRF 1-29 -- Theratechnologies	TP20 -- Avant
ThGRF 1-44 -- Theratechnologies	tPA -- Centocor
Thrombin receptor activating peptide --	trafermin -- Scios
Abbott	TRAIL/Apo2L -- Immunex
thrombomodulin -- Iowa, Novocastra	TRAIL-R1 MAb -- Cambridge Antibody
Thrombopoietin -- Dragon Pharmaceuticals,	Technologies
Genentech	transferrin-binding proteins -- CAMR
thrombopoietin, Pliva -- Recepton	Transforming growth factor-beta-1 --
Thrombospondin 2 --	Genentech
thrombostatin -- Thromgen	transport protein -- Genesis
thymalfasin -- SciClone	Trastuzumab -- Genentech
thymocartin -- Gedeon Richter	TRH -- Ferring
thymosin Alpha1 -- NIH	Triabin -- Schering AG
thyroid stimulating hormone -- Genzyme	Triconal
tlCAM-1 -- Bayer	Triflavin
Tick anticoagulant peptide -- Merck	troponin I -- Boston Life Sciences
TIF -- Xoma	TRP-2 ^A -- NIH
Tifacogin -- Chiron, NIS, Pharmacia	trypsin inhibitor -- Mochida

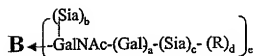
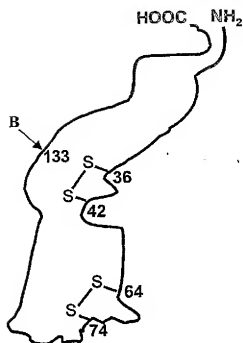
FIG. 28BB

59/497

TSP-1 gene therapy --	Vascular endothelial growth factors -- R&D
TT-232	Systems
TTS-CD2 -- Active Biotech	vascular targeting agents -- Peregrine
Tuberculosis vaccine -- Aventis Pasteur, Genesis	vasopermeation enhancement agents -- Peregrine
Tumor Targeted Superantigens -- Active Biotech -- Pharmacia	vasostatin -- NIH
tumour vaccines -- PhotoCure	VCL -- Bio-Tech. General
tumour-activated prodrug antibody conjugates -- Millennium/ImmunoGen	VEGF -- Genentech, Scios
tumstatin -- ILEX	VEGF inhibitor -- Chugai
Tuvirumab -- Novartis	VEGF-2 -- Human Genome Sciences
TV-4710 -- Teva	VEGF-Trap -- Regeneron
TWEAK receptor -- Immunex	viscumin, recombinant -- Madaus
TXU-PAP	Vitaxin
TY-10721 -- TOA Eiyō	Vitrax -- ISTA Pharmaceuticals
Type I diabetes vaccine -- Research Corp	West Nile virus vaccine -- Bavarian Nordic
Typhoid vaccine CVD 908	WP 652
U 143677 -- Pharmacia	WT1 vaccine -- Corixa
U 81749 -- Pharmacia	WX-293 -- Wilex BioTech.
UA 1248 -- Arizona	WX-360 -- Wilex BioTech.
UGIF -- Sheffield	WX-UK1 -- Wilex BioTech.
UIC 2	XMP-500 -- XOMA
UK 101	XomaZyme-791 -- XOMA
UK-279276 -- Corvas Intl.	XTL 001 -- XTL Biopharmaceuticals
urodilatin -- Pharis	XTL 002 -- XTL Biopharmaceuticals
urofolitrophin -- Sero	yeast delivery system -- GlobImmune
Urokinase -- Abbott	Yersinia pestis vaccine
uteroferin -- Pepgen	YIGSR-Stealth -- Johnson & Johnson
V 20 -- GLYCODesign	Yissum Project No. D-0460 -- Yissum
V2 vasopressin receptor gene therapy vaccines -- Active Biotech	YM 207 -- Yamanouchi
Varicella zoster glycoprotein vaccine -- Research Corporation Technologies	YM 337 -- Protein Design Labs
Varicella zoster virus vaccine livé -- Cantab Pharmaceuticals	Yttrium-90 labelled biotin
Vascular endothelial growth factor -- Genentech, University of California	Yttrium-90-labeled anti-CEA MAb T84.66 -- ZD 0490 -- AstraZeneca
	ziconotide -- Elian
	ZK 157138 -- Berlex Laboratories
	Zollmombab aritox
	Zorcell -- Immune Response
	ZRXL peptides -- Novartis

FIG. 28CC

60/497



a-c, c (independently selected) = 0 or 1;
 d = 0;
 R = modifying group, sialyl or
 oligosialyl

FIG. 29A

61/497

CHO, BHK, 293 cells, Vero expressed G-CSF
a-c, e (independently selected) = 0 or 1; d = 0

- ↓
1. Sialidase
2. CMP-SA-PEG, ST3Gal1

a-d, e (independently selected) = 0 or 1;
R = PEG.

FIG. 29B

Insect cell expressed G-CSF
a, e (independently selected) = 0 or 1;
b, c, d = 0.

- ↓
1. Galactosyltransferase, UDP-Gal
2. CMP-SA-PEG, ST3Gal1

a, c, d, e (independently selected) = 0 or 1; R =
PEG.

FIG. 29C

62/497

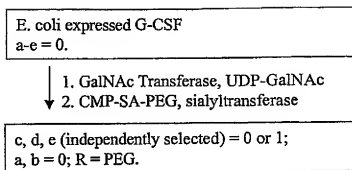


FIG. 29D

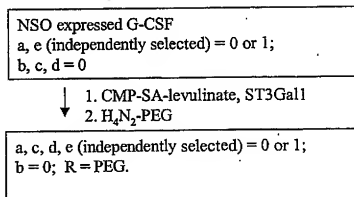


FIG. 29E

63/497

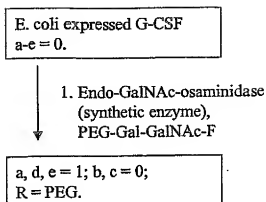


FIG. 29F

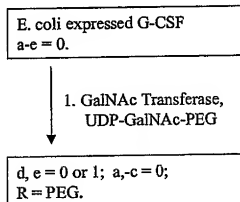
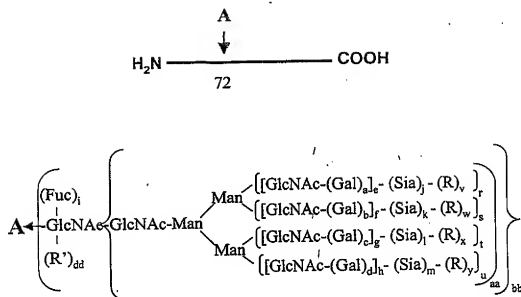


FIG. 29G

64/497



a-d, i, n-u (independently selected) = 0 or 1.

aa, bb, cc, dd, ee (independently selected) = 0 or 1.

e-h (independently selected) = 0 to 6.

j-m (independently selected) = 0 to 20.

v-z = 0; R = modifying group, mannose, oligo-mannose.

R' = H, glycosyl residue, modifying group,
glycoconjugate.

FIG. 30A

65/497

CHO, BHK, 293 cells, Vero expressed
interferon alpha 14C.
a-d, aa, bb = 1; e-h = 1 to 4;
cc, j-m, i, r-u (independently selected) = 0 or 1;
q, n-p, v-z, cc, dd, ee = 0.

1. Sialidase
2. CMP-SA-PEG, ST3Gal3

a-d, aa, bb = 1; e-h = 1 to 4;
bb, cc, i, r-u (independently selected) = 0 or 1;
q, n-p, v-z, cc, dd, ee = 0;
v-y (independently selected) = 1,
when j-m (independently selected) = 1;
R = PEG.

FIG. 30B

Insect cell or fungi expressed interferon alpha-14C.
a-d, f, h, j-q, s, u, v-z, cc, dd, ee = 0;
e, g, i, r, t (independently selected) = 0 or 1;
aa, bb = 1.

1. GNT's 1&2, UDP-GlcNAc
2. Galactosyltransferase, UDP-Gal-PEG

b, d, f, h, j-q, s, u, w, y, z, cc, dd, ee = 0;
a, c, e, g, i, r, t, v, x (independently selected) = 0 or 1;
v, x (independently selected) = 1,
when a, c, (independently selected) = 1;
aa, bb = 1; R = PEG.

FIG. 30C

66/497

Yeast expressed interferon alpha-14C.

a-q, cc, dd, ee, v-z = 0;

r-y (independently selected) = 0 to 1;

aa, bb = 1;

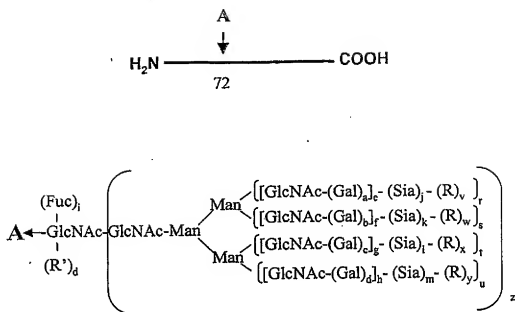
R (branched or linear) = Man, oligomannose or polysaccharide.

- ↓
1. Endo-H
 2. Galactosyltransferase, UDP-Gal
 - 3.. CMP-SA-PEG, ST3Gal3

a-z, bb = 0; aa = 1; R' = -Gal-Sia-PEG.

FIG. 30D

67/497



a-d, i, r-u (independently selected) = 0 or 1.

e-h (independently selected) = 0 to 4.

j-m (independently selected) = 0 or 1.

n, v-y = 0; z = 0 or 1.

R = polymer; R' = sugar, glycoconjugate.

FIG. 30E

68/497

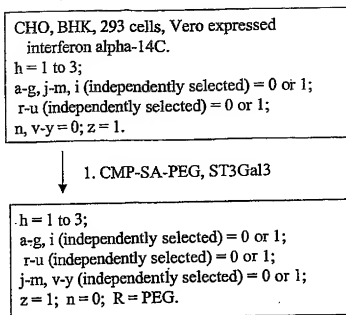


FIG. 30F

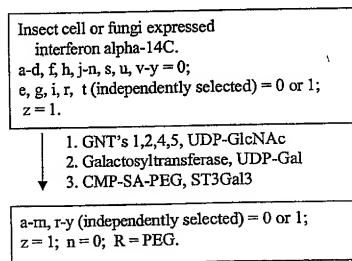


FIG. 30G

69/497

Yeast expressed interferon alpha-14C.
 a-n = 0; r-y (independently selected) = 0 to 1;
 z = 1; R (branched or linear) = Man,
 oligomannose.

1. mannosidases
2. GNT's 1,2,4,5, UDP-GlcNAc
3. Galactosyltransferase, UDP-Gal
4. CMP-SA-PEG, ST3Gal3

a-m, r-y (independently selected) = 0 or 1;
 z = 1; n = 0; R = PEG.

FIG. 30H

NSO expressed interferon alpha 14C.
 a-i, r-u (independently selected) = 0 or 1;
 j-m, n, v-y = 0; z = 1.

1. CMP-SA-levulinate, ST3Gal3,
buffer, salt
2. H₄N₂-PEG

a-i, j-m, r-y (independently selected) = 0 or 1;
 n = 0; z = 1; R = PEG.

FIG. 30I